British Journal of Anaesthesia

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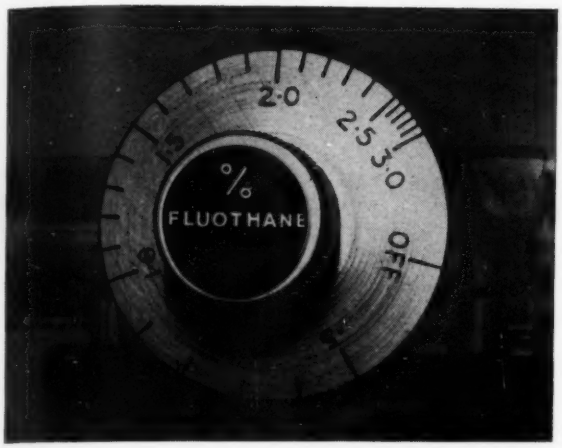

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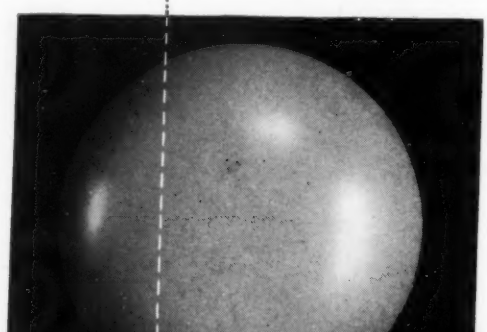

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BRITISH JOURNAL OF ANAESTHESIA

VOL. XXIX No. 10 OCTOBER 1957

EDITORIAL

TEAM RESEARCH

MANY members of the Anaesthetic section of the Manchester Medical Society who listened to Dr. Suckling's address on the discovery of halothane were anxious to have it in print so that they might study it at their leisure, so here it is. In our June editorial we had stressed the value, and indeed the necessity, of team work if progress was to be made in any subject and therefore in anaesthesia as in others. We are fortunate indeed to have so excellent an example of team work to put before our readers, and in lesser degree it is pleasant to have our opinion confirmed. Dr. Suckling says: "Of course, application of these specialized techniques calls for the co-operation of specialists in analytical fields, and one cannot overstress the fact that the discovery and development of even so simple a compound as halothane calls for the co-operation of very many skilled workers, chemists, engineers, physicists—quite apart from the work that is necessary on the biological side. The development of halothane has been very much a team effort." It should be noted that the team work came from the I.C.I. organization. It seems eminently desirable that such team work should be undertaken by the members of the staff of a university. To obtain the interest of chemists, physicists and other scientists in a work of primary importance to anaesthetists would call for considerable co-ordination, it would be very happy if this were forthcoming. A speaker at the recent meeting of the British Association emphasized the need for experts to apply such knowledge as we already possess rather than to acquire new knowledge. Both types are needed and doubtless each individual will find, by a consideration of his natural abilities, to which class he belongs. Though the fascinating story of the discovery of halothane must not be allowed to distract the anaesthetist from his primary duty of anaesthetizing patients, it emphasizes the necessity of his acquiring a deep and wide knowledge of the fundamental sciences upon which practical anaesthesia rests.

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THE NONINFLAMMABILITY OF FLUOTHANE

BY

G. H. F. SEIFLOW

Imperial Chemical Industries Ltd., General Chemicals Division, Research Department

ONE of the important advantages claimed for halothane (Fluothane) is that it is noninflammable. The experiments described below give the evidence on which this claim is based.

METHODS

Observations on mixtures of halothane vapour with oxygen, with oxygen and nitrous oxide, and with oxygen and ether, have been made by methods similar to those developed by the U.S. Bureau of Mines.

For concentrations of halothane up to the saturation vapour pressure at room temperature the method used was essentially that described by Jones, Kennedy and Miller (1942). The ignition vessel is a vertical tube 150 cm high by 5 cm in diameter. The tube is evacuated, and the gases or vapours to be tested are admitted, their relative proportions being measured in terms of their partial pressures. The contents of the tube are then thoroughly mixed; for the present work a loosely fitting stirrer was used, consisting of two perforated polythene discs mounted at each end of a small tinplate cylinder and operated magnetically. When the mixture is considered to be homogeneous, a gas flame from a narrow jet is applied to the lower end of the tube. Inflammability is unmistakable; for example there may be a detonation, as with ether and oxygen, or a band of flame may travel up the tube, as with butane and oxygen.

For concentrations above saturation at room temperature it is simpler to prepare oxygen saturated with halothane at known temperatures, rather than to control the temperature of the apparatus described above, and the method adopted was that described by Jones, Scott and Miller (1942). The ignition vessel in this case is a vertical glass tube 12 inches high and 1 inch in diameter. In the bottom is a 2-inch depth of the liquid under test with about an inch depth of glass beads to promote saturation of the gas. The tube is immersed in a thermostatically controlled water bath. Two platinum electrodes sealed into the tube about an inch above the level of the liquid are connected to an induction coil capable of giving a 3-inch spark. The oxygen is bubbled slowly through the liquid for about 30 minutes, to ensure that the vapour space is filled with saturated vapour. A spark is then passed between the electrodes, and the presence or absence of a detonation or of a flame noted.

Adequate safety precautions were, of course, taken during all these experiments.

RESULTS

Halothane and Oxygen

Using the first apparatus at room temperature, observations were made on mixtures of halothane vapour and oxygen at eleven different proportions from 0.1 per cent halothane by volume up to about 33 per cent, the saturation concentration at the ambient temperature. In no case was there any evidence of burning.

Using the second apparatus, observations on oxygen saturated with halothane vapour were made at every 5°C from 20° to 45°C and at several different temperatures between 45°C and the boiling point; the range of concentrations obtained was from 32 per cent to 100 per cent halothane by volume. Again in no case was there any evidence of burning.

Halothane, Oxygen and Nitrous Oxide

Using the first apparatus, observations were made on six different mixtures containing between 0.1 per cent and 10 per cent halothane by volume, the remainder being a 50/50 mixture of oxygen

and nitrous oxide. In no case was there any evidence of burning.

Halothane, Oxygen and Ether

Finally, using the first apparatus, observations were made on inflammable mixtures of ether and oxygen, containing about 3 per cent ether by volume, diluted with nitrogen and with halothane. It was found that volume for volume halothane had the same effect as nitrogen, i.e. it behaved simply as an inert diluent.

CONCLUSIONS

The observations described show that mixtures of halothane and oxygen in any proportions are noninflammable, that mixtures of halothane, oxygen and nitrous oxide in proportions likely to occur in anaesthetic practice are noninflammable, and that halothane acts as an inert diluent when added to an inflammable ether/oxygen mixture. It is reasonable to conclude therefore that halothane is noninflammable under all ordinary circumstances.

SUMMARY

Using apparatus and methods based on those developed by the U.S. Bureau of Mines it is shown that mixtures of halothane and oxygen containing between 0.1 per cent and 100 per cent halothane by volume, and mixtures of halothane and 50/50 oxygen and nitrous oxide containing between 0.1 per cent and 10 per cent halothane, are noninflammable, and that halothane acts as an inert diluent for inflammable mixtures of ether and oxygen containing 3 per cent ether by volume. It is concluded therefore that halothane is noninflammable under all ordinary circumstances.

ACKNOWLEDGMENT

The apparatus described was constructed by Mr. J. Adams, who also made most of the measurements.

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Jones, G. W., Kennedy, R. E., and Miller, W. E. (1942). Limits of Inflammability and Ignition Temperature of Ethyl Mercaptan in Air. *Bureau of Mines Report of Investigations* 3648.

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Brit. J. Anaesth. (1957), **29**, 440

ABNORMAL RESPONSES TO BARBITURATES*

BY

JOHN W. DUNDEE

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ALTHOUGH the desired action of barbiturates is on the central nervous system, the drugs act to some extent on all the structures of the body. Diffusion to non-nervous tissues takes place very rapidly, especially after intravenous injection, and most of the effects of the drugs are evident almost as soon as consciousness is lost.

The actions of barbiturates on structures other than the central nervous system result in most of the abnormal responses and dangers of these drugs. Susceptibility to various systems to barbiturates differs in certain pathological states and occasionally the dose necessary to produce loss of consciousness may be contra-indicated because of its depressant effects on the myocardium or peripheral vascular system.

True idiosyncrasy to the barbiturates is very rare and there are few absolute contra-indications to their use. Most abnormal responses are the result of overdosage. This may be from an excessive dose given to a fit subject, or, more commonly, a so-called "normal dose" administered to a susceptible patient. This latter applies particularly to the action on the cardiovascular system, and to a lesser extent on the respiratory system.

In the subsequent discussion emphasis will be placed on those barbiturates and thiobarbiturates which are commonly given by the intravenous route.

CENTRAL NERVOUS SYSTEM

Onset of Anaesthesia.

Although the drugs used for induction of anaesthesia are classified as rapid acting, there is a wide variation in the rate of onset of anaesthesia with any given drug in different subjects. This variation is only related to dosage with small induction doses. Figure 1 illustrates the variation in 156 fit subjects, all of whom received over 5 seconds a dose of thiopentone, adequate to produce eventually loss of consciousness. The time was noted from the end of the injection until the patient stopped counting. This is not as unreliable an endpoint as is commonly believed; it usually occurs one-third of the way between e.e.g. levels 1 and 2. The average time was 16.4 seconds, with variations of between 9 and 35 seconds. If patients with an abnormal cardiovascular system had been included in this study, this variation would probably have been greater.

Figure 1 illustrates that, under clinical as opposed to laboratory conditions, there is a wide variation in the normal response to barbiturates. Data presented by Hunter (1947) places the average onset of narcosis after 150 mg thiopentone and 300 mg hexobarbitone as 15.5 and 16 seconds respectively. Without qualifications of these figures one would consider the patients at both extremes of the range in figure 1 as showing

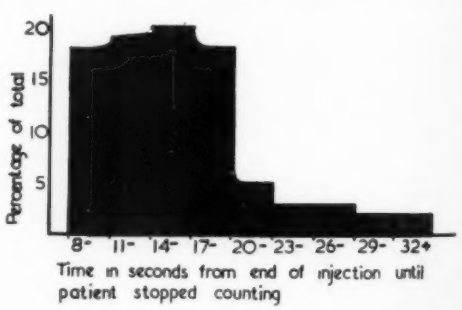

FIG. 1

Time of onset of anaesthesia following thiopentone in 156 patients.

* Paper read to the Annual Meeting of the Anaesthetic Section of the British Medical Association, Newcastle upon Tyne, July 1957.

an abnormal response to the barbiturates. However, as with many other so-called abnormal responses, there is a simple explanation of the variation.

During the summer of 1955, I was fortunate to work at the air-conditioned hospital of the University of Pennsylvania, with operating theatre temperatures of 72–74°F (22–23°C), and also at the Philadelphia General Hospital with theatre temperatures of 84–90°F (29–32°C) without air conditioning. Figure 2 shows a comparison of the time of onset of narcosis from different doses of thiopentone and pentobarbitone at the different environmental temperatures. Dose is not a factor in determining the time of onset of narcosis with the injection of amounts greater than 3.5 mg/kg of either drug. Table I shows that the differences in time of onset of both drugs is significantly shorter at the higher environmental temperature. At any given temperature it also reveals a more rapid onset of anaesthesia with thiopentone than with pentobarbitone, which is statistically significant.

TABLE I

Time of Onset of Anaesthesia with Doses of Thiopentone and Pentobarbitone greater than 3.5 mg/kg.

Room temperature	Drug	No. of cases	Average time in seconds
22–23°C	Thiopentone	22	19.7 ± 0.90
	Pentobarbitone	17	33.2 ± 3.10
29–32°C	Thiopentone	22	14..9 ± 0.67
	Pentobarbitone	17	21.3 ± 1.64

There is a significant difference between the time of onset of anaesthesia with thiopentone and pentobarbitone at 22–23°C ($t=6.08$) and at 29–32°C ($t=5.12$) and also between the time of onset of anaesthesia with thiopentone ($t=6.12$) and pentobarbitone ($t=5.00$) at the different environmental temperatures.

The relationship of these differences to the environmental temperature is probably related to a change in forearm blood flow, due to increased

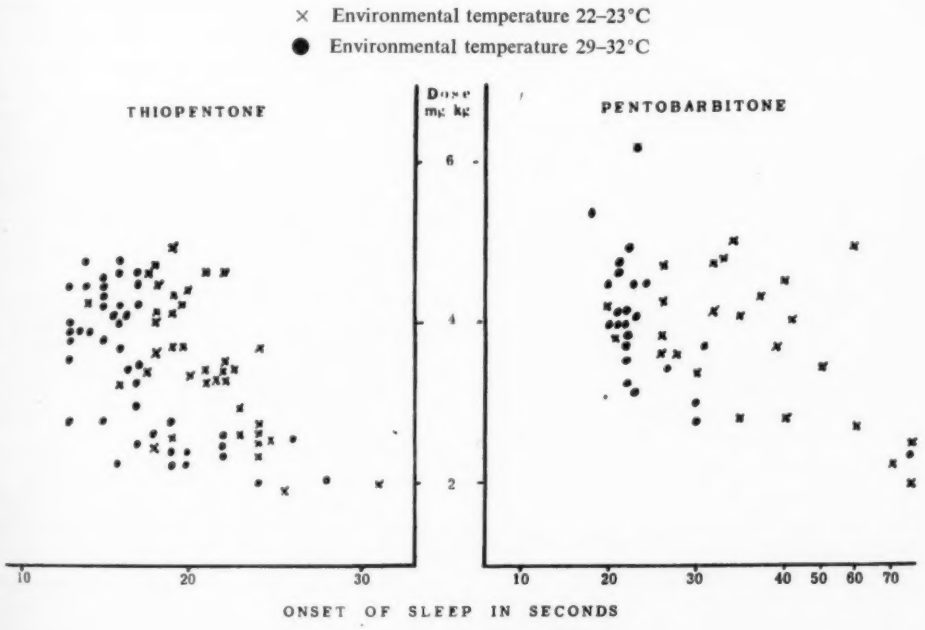

FIG. 2

Time of onset of anaesthesia with thiopentone and pentobarbitone at different environmental temperatures.

cardiac output and vasodilatation at the higher temperature. This latter possibility was investigated by producing maximum vasodilatation in one limb only at the lower environmental temperature, prior to injection. A sphygmomanometer cuff was inflated to beyond systolic blood pressure for one minute and then released. Figure 3 shows that, by this manoeuvre, the onset of unconsciousness at low temperatures could be approximated to that at higher temperatures, and suggests that the degree of peripheral vasodilatation in a limb is an important factor in determining the rate of onset of anaesthesia with intravenous barbiturates.

The onset of anaesthesia has been discussed at length because of its importance in avoiding overdosage with barbiturates. If a drug is given at a fixed rate of 1 ml of 2.5 per cent solution per second, about 150 mg more would have been injected before the patient stopped counting at the hospital with the lower operating theatre

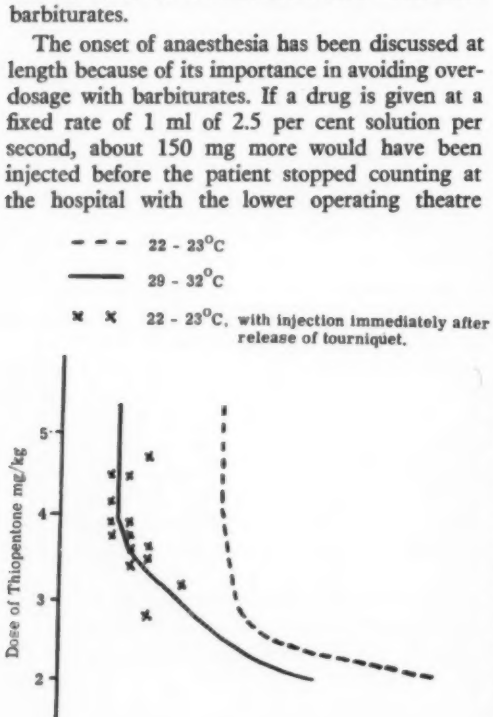

FIG. 3

Time of onset of anaesthesia with thiopentone at different environmental temperatures and following release of tourniquet in patients at lower environmental temperatures.

temperature as compared with that in the same patient in the higher environmental temperature. This difference may be of grave importance in ill patients. Ruddell (1953) states that in hot weather in the tropics the onset of anaesthesia with hexobarbitone is more rapid than in the cold weather, but no attention seems to have been paid to this point. Hunter (1947) mentions prolongation of the time of onset of intravenous barbiturate narcosis in patients with myocardial failure and allowance must also be made for this in such subjects.

Prolonged Narcosis.

This abnormal response, which is preventable, can be due to a variety of causes. Interference with redistribution occurs in such conditions as uraemia (where there is also a decrease in the plasma binding) and peripheral circulatory failure. Decreased rate of detoxication is a less important cause, but the duration of narcosis from large doses of thiopentone is increased in severe liver damage (Dundee, 1956). One must also remember the marked increase in the half-life of thiopentone which Rink et al. (1956) have described at low temperatures.

Of greater clinical importance, because it may occur unexpectedly, is synergism between the barbiturates and other drugs. Patients with peripheral circulatory failure may have unabsorbed depots of morphia which are released into the general circulation as the result of resuscitation or the peripheral vasodilatation produced by the barbiturate. Not only will this cause prolonged narcosis, but severe (and apparently unexplained) respiratory depression may ensue. The potentiation of both oral and intravenous barbiturates by chlorpromazine and similar drugs is also a potential hazard because of the increasing use of tranquillizers and the fact that their administration may not be mentioned to the anaesthetist.

Supplementation of light barbiturate narcosis by intravenous analgesics can cause an apparent increase in the duration of action of the barbiturate. If sufficient dose of analgesic has been given to produce a quiet operating field with some degree of respiratory depression during skin suture when the stimulation has ceased and the patient has returned to the quiet of the ward,

there will almost certainly be prolonged narcosis and possibly dangerous respiratory depression. Re-induction of anaesthesia has even been described by the too early and too liberal use of postoperative analgesics.

Increase in the duration of barbiturate narcosis occurs in severe anaemia, but is unlikely to be of such severity as to endanger life. When used to control convulsions barbiturates have an exaggerated action, which is probably due to increased activity of cerebral cells or to the cause of the convulsion itself.

Stimulant Action.

Although phenobarbitone and other barbiturates are known to be potent anticonvulsants, chemically they are closely related to convulsant drugs. The presence of six carbon atoms in the 5, 5[1] side chains, alkylation of the 1 and 3 nitrogens or sulphuration of the 2 position can convert some barbiturates into convulsants. Apart from the abnormal muscle movements which seem to be an inherent property of drugs such as hexobarbitone, N-methyl (or ethyl) thiobarbiturates and Lilly 25398, the so-called "convulsive properties" of barbiturates are probably not related to their chemical structure but rather are a manifestation of their lack of analgesic action. Movement of limbs during induction and the uncontrolled delirium seen postoperatively in children, who have received barbiturates before or during operation, can be considered to be analogous to the hyperirritability and excitement sometimes seen during second stage anaesthesia with the volatile agents. Both these complications can be minimized by the appropriate use of analgesics. This lack of analgesic action is probably responsible also for the high incidence of shivering which Smith et al. (1955) have described during recovery from thiopentone anaesthesia.

Electrolyte Disturbances.

All clinicians are aware of the exquisite sensitivity to barbiturates that occurs in patients with electrolyte disturbances. Such cases include acute intestinal obstruction, peritonitis and starvation. These patients fall asleep after minute doses and narcosis may be more prolonged than one would expect. Foster (1956) has suggested that the hypokalaemia seen in such conditions leads to decreased permeability of the blood-brain barrier, which could explain their response to barbiturates. In support of this hypothesis is the sensitivity to all anaesthetic agents reported by Hardy et al. (1953) in induced hypokalaemia. On the other hand, Lamson and Greig (1953) have shown that excess amounts of potassium also potentiate the action of barbiturates.

CARDIOVASCULAR SYSTEM

Gould (1951) has admirably described the importance of the cardiovascular effects of barbiturates in his statement that "sensitivity to intravenous drugs depends on the effect of that sensitivity on the circulation . . . the circulation always being primarily affected". This is shown by the recent report on anaesthetic deaths by the Association of Anaesthetists of Great Britain and Ireland (Edwards et al., 1956). Circulatory failure following intravenous barbiturate injection accounted for 19 per cent of the deaths and was the second most commonly reported cause of death.

A slight blood pressure fall is the normal response to the barbiturates. Factors which lead to abnormal falls or prolonged hypotension can best be discussed by first reviewing briefly the cardiovascular effects of these drugs. There are many conflicting reports in the literature on this subject, but the following facts are substantiated by accurate laboratory and clinical observations.

Thiopentone is a depressant of the dog heart-lung preparation (Prime and Gray, 1952), the degree of depression being proportional to the concentration of the drug (Price and Helrich, 1955). These latter workers found that the action of thiopentone was less than that of equivalent concentrations of ether, cyclopropane or nitrous oxide. A fall in the blood pH decreases the efficiency of the isolated dog's myocardium.

Price et al. (1957) found a linear relationship between blood thiopentone concentration and the degree of arterial hypotension in man, while Feldman et al. (1955) found that this varied with the depth of anaesthesia, as measured by the electroencephalogram. The fall in arterial blood pressure during induction of anaesthesia is most marked after rapid injection of the drug and in hyper-

tensive patients. Feldman et al. (1955) found that the maximum blood pressure fall occurred within 90 seconds of injection. There is a consistent fall in the cardiac index after induction of anaesthesia with thiopentone (Elder et al., 1955), although it may not be of such severity as to be detected by the ballistocardiograph ten minutes later (Pollock et al., 1955).

Since the venous pressure does not rise during thiopentone anaesthesia, it is unlikely that myocardial insufficiency is a major cause of the fall in cardiac index. This latter has been found by Feldman and his colleagues to be proportional to the fall in central blood volume. From this they conclude that the hypotension results from changes due to vasodilatation, pooling of blood in the periphery and a decreased venous return. Thiopentone has also been found by Price et al. (1952) to modify the vasomotor response to positive pressure inflation of the lungs.

This experimental data is supported by a wealth of clinical observations (see Dundee, 1956) showing that the unhealthy cardiovascular system is extremely susceptible to the depressant effects of the barbiturates. This degree of sensitivity is proportional to the amount of circulatory impairment or myocardial disease. Cardiac hypoxia from hypotension further decreases the efficiency of the heart and a vicious circle is set up.

From these considerations one can expect abnormal responses to barbiturates in the following circumstances:

(*a*) in patients who cannot tolerate peripheral vasodilatation, because of deficient blood volume;
(*b*) where there is an already damaged myocardium from any cause;
(*c*) in hypertensive subjects;
(*d*) following rapid injections of the barbiturates.

It must be remembered that lightening of the depth of anaesthesia is not necessarily accompanied by a return of the blood pressure to normal. Hypotension can persist for long periods after the return of consciousness.

RESPIRATORY SYSTEM

Abnormal responses of the respiratory system to barbiturates can either consist of severe respiratory depression or take the form of irritative phenomena such as coughing, sneezing, hiccough or bronchospasm. Prolonged and profound respiratory depression is not common following the cautious administration of barbiturates and is usually due to overdosage. Once it occurs and the lungs are inflated with oxygen, there may be difficulty in re-establishing spontaneous respiration, because of the shift of the control of respiration from the chemoreceptors and respiratory centre to hypoxia, as a result of the barbiturates. Anaesthesia will have to be lightened until the response of the respiratory centre to carbon dioxide returns. One of the most common causes of prolonged respiratory depression following barbiturates is the synergism between these drugs and the opiates (Helrich et al., 1956).

The mechanism of such abnormal responses as coughing and hiccough is not known. They can occur immediately after injection before the loss of consciousness. In this respect they resemble the initial stimulation of respiration caused by barbiturates, which, because of its temporal relation to the cerebral effects of the drugs as judged by the electro-encephalogram, is probably due to reflex stimulation from the carotid body. With the exception of hiccough, these phenomena occur in the lighter planes of anaesthesia. By contrast, hiccough can occur in apnoeic (or even curarized) patients. Coughing, sneezing and bronchospasm occur more frequently in chronic bronchitics, asthmatics and vagotonic subjects. The presence of excess mucus or foreign bodies in the respiratory tract are also predisposing factors.

There is a marked variation in the incidence of abnormal respiratory phenomena with different barbiturates. Thiopentone, thialbarbitone and thiamylal are the least troublesome, while a high incidence has been observed with the newer, and reputedly shorter acting, buthalitone and methothiourate. This difference may be a specific difference in the action of the drugs or a manifestation of a more rapid return to lighter planes of anaesthesia with the newer drugs.

OTHER ABNORMAL REACTIONS

Idiosyncrasy to the barbiturates, as manifested by skin reactions, is very rare. Phenobarbitone seems

to be the worst offender and skin rashes are of no clinical importance when occurring during intravenous anaesthesia.

Patients with porphyria or photosensitivity react to barbiturates by the passage of reddish coloured urine, which may be followed by an attack of acute porphyria. Dundee and Riding (1955) from an analysis of published cases, have pointed out the high mortality which follows the use of oral and intravenous barbiturates in porphyria.

A recent publication by Bourke and Zuck (1957) has again focused attention on the abnormal responses to thiopentone by patients with dystrophia myotonia, as first described by the author in 1952. Respiratory depression follows very small doses of the barbiturate in these patients and it is advisable to avoid their use completely.

Adrenocortical insufficiency as a cause of abnormal responses, not only to barbiturates but to all anaesthetic agents, is of great topical interest. These patients are prone to hypotension and respiratory depression as well as prolongation of narcosis. With increasing use of oral therapy with hydrocortisone and prednisolone, anaesthetists must be aware of the possibility of undetected drug-induced depression of adrenocortical function.

PROPHYLAXIS

Abnormal responses to barbiturates can best be avoided by appreciation of the limitation of these drugs which are primarily hypnotic with very little analgesic action. They should be used primarily for induction of anaesthesia, except for the briefest procedures. Where prolonged anaesthesia or relaxation is required, use should be made of analgesics and muscle relaxants, with small supplementary doses of barbiturates as required. Studies of the phenomenon of acute tolerance to thiopentone by Dundee, Price and Dripps (1956) have shown that much smaller doses are needed for the induction of anaesthesia than those commonly employed in this country. The slow injection of dilute solutions will minimize the effects of barbiturates on the cardiovascular and respiratory systems and above all the anaesthetists should remember Nosworthy's remark that "overdosage is fatally easy".

ACKNOWLEDGMENTS

I am indebted to Drs. H. L. Price and E. H. Connor for permission to report the observations on the time of onset of anaesthesia and for their assistance during this study.

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BOOK REVIEW

Medical Annual 1957. Edited by Sir Henry Tidy and R. Milnes Walker. Published by John Wright & Sons Ltd., Bristol. Price 38*s*. 6*d*.

Dr. Langton Hewer again writes the article on "Anaesthesia and Analgesia". It calls attention to the report issued by the committee on the causes of deaths during anaesthesia, on the increased risk of operation on those who have been taking cortisone, and the treatment of inadvertent intra-arterial injection. A number of recently introduced drugs are referred to—Pacatal, Viadril, Nisentil. Mention is also made of the EMO, a simplified portable version of the Oxford Vaporizer No. 1. This very short account is supplemented by Dr. C. S. Russell in an even shorter one on the best method of anaesthesia for the woman in labour. These short articles do not cover the whole of the subject. A special article on "Hypothermia" by T. C. Gray, with 72 references, will give some idea of the widespread interest in the subject and Dr. Gray's preoccupation with and work on hypothermia. Here readers will find how to apply it, the indications for it, the physiological effects of and the dangers accompanying. If the reader's interest extends further the long list of references will supply him with all the latest information. A short article by Dr. G. K. Harrison on the use of hypothermia for the inter-atrial septal defect operation concludes the series on Anaesthesia. It by no means exhausts the subjects of interest to the anaesthetist. Of these others, special mention should be made of Dr. Douglas's article on "The Modern Theory of Blood Coagulation" and also that on "Prostatic Enlargement" by G. W. Riches.

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Brit. J. Anaesth. (1957), **29**, 447

BRONCHOGRAPHY UNDER ETHER

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IN this country, as in many others, bronchography has become a routine procedure. In children it is usually performed under general anaesthesia and many techniques have been described. Since 1948 the Liverpool Thoracic Surgical Unit has favoured the open ether technique described by Temple and Gray (1950) and there are now 500 cases available for review. The method appears to be a satisfactory one and has certain possible advantages over alternative techniques.

HISTORY

The first deliberate attempts at bronchography were made by Chevalier Jackson who, beginning in 1905, experimented with the introduction of bismuth oxide through the bronchoscope (Jackson, 1907). Bismuth oxide was neither entirely safe nor entirely satisfactory, and the illustrative plate to a later article (Jackson, 1918) shows that the standard of the films was not high. Thorium oxide was tried in 1919 (Weingaertner, 1919) and in 1922 the idea of an oily solution occurred to Lynah and Stewart (1922) who used an emulsion of bismuth subcarbonate and olive oil. The possibilities of iodine had been noted in 1917 by Yankhauer, who observed that after the introduction of iodine into bronchiectatic cavities for therapeutic purposes he was able to see the cavities outlined radiographically (Yankhauer, 1917). Five years later Sicard and Forestier (1922) combined the advantages of iodine with those of an oily base, and introduced lipiodol. This was the first really satisfactory agent and after 1922 iodized poppy seed oil (lipiodol, neohydriol, iodatol) held the field for over thirty years.

The chief disadvantages of lipiodol are its tendency to produce alveolar filling and its persistence in the lungs for weeks after its introduction. In some clinics a mixture of iodized oil and sulphonamide (5 g sulphanilamide powder in 20 ml) attained considerable popularity; it offers the advantage of greatly reduced alveolar filling and residual opacity, but it is a difficult solution to inject on account of its viscosity and occasional toxic effects are seen from the sulphonamide content (Belcher and Grant, 1955). After much preliminary work a satisfactory water soluble medium, dionosyl, was introduced in this country in 1952 (Don, 1952). Dionosyl is absorbed from the lungs in a matter of days, and excreted without liberating free iodine: its toxicity is thus extremely low, but it is considerably more irritant to the bronchial tree than lipiodol. A preliminary report of its use under anaesthesia appeared in 1953 (Rendle-Short, 1953). The same organic iodine base can be obtained in an arachis oil suspension, as dionosyl 60 per cent oily. This preparation retains the advantage of rapid absorption, and is at the same time much less irritant and less liable to produce alveolar filling. With the general anaesthetic technique described in this paper it was very soon found to be vastly superior to the watery preparation.

In the adult, bronchography is almost always carried out under local anaesthesia and a very extensive literature has accumulated on different methods of introducing the radio-opaque substance. The details of most of these methods are not relevant to the present discussion; an authoritative contemporary review of early bronchographic practice is given by Oschner and Nesbit (1928) and a more up to date summary may be found in Huizinga and Smelt's book *Bronchography* (Huizinga and Smelt, 1950). There is one

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method, however, the so-called "Verschluck-methode" (choking method) which deserves further consideration. It is a method that arose from the chance observation that during barium examinations of the oesophagus some outlining of the bronchial tree occasionally occurred. Oschner and Nesbit (1928) describe how such an incident was witnessed in Zürich on a patient whose pharynx had been cocainized for oesophagoscopy: when the films were seen it was thought at first that the patient must have a carcinomatous tracheo-oesophageal fistula, but it was soon discovered that after complete anaesthetization of the pharynx any foreign material would enter the larynx rather than the oesophagus (Nather and Sgalitzer, 1925). This discovery was exploited as a routine method of bronchography and Oschner and Nesbit were able to report over 700 cases without untoward signs or symptoms. Their technique, which they called the "passive method", was simply to cocainize the pharynx and larynx and ask the patient to hold the warmed lipiodol in his mouth and take a series of short breaths. Some degree of posturing was attempted and great stress was laid on the importance of fluoroscopic control.

In children bronchography can be performed without any form of anaesthesia at all (Huizinga and Smelt, 1950), but the practice is not acceptable in this country, firstly because the violent coughing produces alveolar filling and secondly because the psychological effect is bad (Brock, 1950). On the other hand, if the oil is gently run into the nose from a syringe, after the manner of Forestier and Leroux (1935), and if sufficient time and patience are expended the child need not object to the procedure at all and good films can be obtained (Bickford, 1956). Satisfactory results have been achieved under hypnosis (Kasasian, 1957), and with care and understanding surprisingly young children will tolerate local anaesthetic techniques (Sita-Lumsden, 1950; Belcher and Grant, 1955). Nevertheless the usual choice for bronchography in children is some form of general anaesthesia.

The first report of the use of general anaesthesia for bronchography was that of Jacoby and Keats (1938). They described how they had begun experimenting with various methods in 1935, including cricothyroid injection, and how Keats had discovered in the same year that it was possible to obtain very satisfactory results simply by pouring the oil into the mouth under deep anaesthesia. By 1938 they were able to report the results of a small series of cases in which they had used rectal bromethol followed by a slow open ether induction. When the child was fully anaesthetized a Doyen's gag was inserted and the tongue was held out; the child was inclined to the side to be filled and the oil was injected through a curved cannula near the posterior pharyngeal wall. The child was kept semi-sitting for half a minute and then positioned and left for two to three minutes. There were no complications even though some of the patients had up to three bronchograms. The authors remarked that coughing during the anaesthetic usually indicated the presence of secretion and it was their practice to return such cases to the ward for further postural drainage. They did not distinguish between cases with loose secretion in the main bronchi and those with tenacious and often "silent" secretion in the smaller divisions. The further comment was made that the child usually regained his reflexes by the time he was back in bed, and to this end the patients were turned on their sides and given 30 per cent carbon dioxide. It is very probable that this delay in recovery, which would nowadays generally be regarded as unacceptable, was related to the deliberate slowness of the induction. No illustrative films were shown and no figures were given.

Lyons (1939) reviewed the methods of bronchography and discussed their applicability to children. He described a "combined technique" using bromethol followed by topical analgesia of the larynx and nitrous oxide-oxygen anaesthesia with nasal intubation. The trachea was sucked out, the child was positioned and the lipiodol was introduced by means of a catheter passed through the endotracheal tube under fluoroscopic control. Further suction was employed after the films were taken. The results were said to be more satisfactory than with any other technique, but no figures were given. The article was illustrated by one film of a right lower lobe bronchogram which was not outstandingly good. In the same year Pearson

and Thornton (1939) in this country described a similar method. They also used an endotracheal tube with an inner catheter, which was introduced through a special side hole. Rectal paraldehyde was followed by cocainization, ethyl chloride, open ether, intubation and packing of the pharynx and maintenance with nitrous oxide and oxygen. No figures were given. Baker (1941), after trying several methods, came to the conclusion that the most satisfactory technique was to introduce the oil through a catheter lying a quarter-inch beyond the tip of an endotracheal tube; he used bromethol, and he pointed out that bronchial intubation was unnecessary. Considerable attention was paid to posturing but no illustrative films were shown, and the comment that "it is rarely necessary to fill the upper lobes" suggests that the results were not entirely satisfactory.

The idea of introducing the oil through a catheter within an endotracheal tube was criticized by Macintosh and Mushin (1950). They pointed out that in the small respiratory passages of a child this practice results in a relatively enormous reduction in the effective diameter of the airway. To avoid this difficulty they used a small catheter for the oil, without an endotracheal tube. Way and James (1950) described the use of a special endotracheal tube with a side-tube outside its lumen through which the oil could be introduced. Their anaesthetic technique consisted of giving thiopentone 0.5 to 1 gram to children of 4 to 12 years of age, followed by 5 per cent cocaine to the larynx. No figures were given, and the choice of anaesthetic agents and dosage were soon criticized (Wright, 1950). Armstrong Davison (1950) pointed out that an ordinary cuffed endotracheal tube could easily be adapted for this purpose by cutting off the distal end just proximal to the cuff. He advocated passing the tube into the main bronchus of the side to be filled, and warming the oil to facilitate injection.

Spacek and Byrne (1950) described the use of a mixture of 1 gram of 5 per cent thiopentone with 80 mg of gallamine, injected on the basis of 1 ml per year of age, followed by intubation and direct introduction of the dye through the endotracheal tube. Maintenance was with cyclopropane and oxygen using a Cope's absorber. No figures or illustrations were given but it was said that the authors had never failed to obtain satisfactory bronchograms for diagnostic purposes. Rollason (1950) used a similar technique with a mixture of thiopentone and tubocurarine, giving neostigmine at the end of the procedure if necessary. He described the method as being "satisfactory", with no explosion risk and a prompt return of reflexes. In the same year a preliminary communication appeared on the method which forms the basis of this paper (Temple and Gray, 1950). The authors mentioned having seen Allison demonstrate the way in which lipiodol will enter the larynx under anaesthesia and stated that they had adopted a simple "drowning technique" under open ether as a routine method of bronchography. They did not refer to the Verschluckmethode of earlier writers and Keats's prior discovery was not quoted. At that time the method had been used in about 250 cases and "very good bronchograms were obtained". In contrast to Jacoby and Keats (1938) the importance of a rapid induction was stressed.

Macintosh and Mushin's use of a catheter without an endotracheal tube was amplified in an article by Mushin and Lake (1951). They reviewed the advantages and disadvantages of several methods and went on to discuss their technique, which consisted of bromethol and atropine followed by open trichloroethylene or nitrous oxide-oxygen-trichloroethylene and spraying of the vocal chords with 5 per cent cocaine. A gum elastic or polythene catheter was then inserted into the trachea and more cocaine injected through it, the dose being estimated on a weight basis. No results were given at all. Wood and Astley (1952), like Spacek and Byrne (1950) and Rollason (1950), adopted the opposite approach of using an endotracheal tube without a catheter for introducing the dye. They used suction through the endotracheal tube to clear the respiratory passages before introducing the oil, and claimed that with this precaution prolonged preradiological postural drainage was unnecessary. The technique was used in over 200 examinations and "may be performed adequately where other methods fail". Although the advisability of removing secretion from the airway is not in doubt, it is unlikely on theoretical grounds that blind suction through an endotracheal tube could be

relied on to remove all secretion of the kind that might interfere with bronchographic filling.

A variation of the "drowning technique" was described in 1953, in which the oil was injected from a syringe into a Phillip's airway (Griffiths, Culbert and Sher, 1953). Nitrous oxide, oxygen and chloroform were used, with the addition of carbon dioxide, and after injection of the oil the mask was replaced and the child was turned on to the side to be filled. No figures, pictures or other data were presented but the method was said to give "good results". It was also in 1953 that the first report of the use of dionosyl (watery) under anaesthesia was published, when Rendle-Short (1953) described a small series of cases anaesthetized by Doctor Barbara Roberts. Gallamine triethiodide was used for some of the cases and from this time on there was an increasing number of reports in the literature of methods involving the use of muscle relaxants.

A paper from Great Ormond Street described the use of thiopentone and gallamine with intubation and posturing of the child *before* the dye was introduced (Browne, Lovel, Raulin and Rickard, 1953). The right side was filled first, the child being apnoeic all the time. The dye was then sucked out and the left side could be filled if necessary. It was admitted that there may be difficulty with finding veins in the case of a fat child and that in view of the apnoea the procedure was completed as expeditiously as possible. The technique of posturing was illustrated by drawings. Two hundred cases had been dealt with in this way with no deaths or complications, and the method was stated to be more satisfactory than others. Good bronchograms were regularly obtained, "there being no tendency to alveolar filling". No further figures or details were given.

Love and Morrow (1954) used a thiopentone or nitrous oxide induction followed by suxamethonium 7 mg/stone (6.3 kg) of body weight. The child was then inflated with oxygen and bronchoscopy and suction were carried out as a routine. Following this an oral tube was passed and maintenance was effected with nitrous oxide-oxygen and sometimes trichloroethylene. The dye was then injected through a catheter projecting just beyond the endotracheal tube, it being argued that the disadvantage of the two concentric tubes was offset by the quiescence of the bronchial and respiratory musculature. Posturing was carried out and the child was inflated except during the exposure of the films. In 200 cases there were no deaths and no serious complications, and the radiological results were "satisfactory". Illustrative films were not shown. Belcher and Grant (1955) recommended either thiopentone and suxamethonium or nitrous oxide-oxygen-ether, in either case with oral intubation using a Cobb type connection. After preliminary suction the dye was injected through a gum elastic catheter half the diameter of the endotracheal tube, the patient being already laid on the side to be filled. Posturing was then carried out and as soon as the films had been taken the catheter was removed and replaced by a larger, clean one through which the dye could be sucked out. The head was then kept down until the child began coughing.

Jooste, from South Africa, reported a technique which had been used for adult cases as well as children, there being some difficulty in obtaining sufficient co-operation for local methods in the case of certain negro patients (Jooste, 1955). Thiopentone was given with 25 mg suxamethonium, and, after inflation with oxygen, bronchoscopy and suction were carried out. During this procedure the duration of apnoea was noted for subsequent reference, and also the time taken for cyanosis to appear (it must be assumed that this latter was used only as an approximate guide since many of the patients were negroes and there is no mention of haemoglobin estimations being carried out). The patient was then intubated and given more suxamethonium; for the intubation a smallish Magill tube was used, with a hole near the proximal end through which a catheter could be inserted, and it was arranged to lie with the bevel pointing upwards and the tip one inch above the carina. The patient was now maintained by means of intratracheal insufflation of oxygen, the suxamethonium being repeated when necessary in order to give complete relaxation. The author stated that the period of apnoea was kept down to ten minutes and that although he would interrupt the procedure in the event of cyanosis he had not needed to do so in over 100 cases. A clinical investigation showed that under compar-

able circumstances the percentage oxygen saturation of the blood remained satisfactory during ten minutes insufflation, but the carbon dioxide level, as would be expected, rose progressively.

COMMENT

It can be seen from this summary of the literature that there is no ideal method of bronchography under anaesthesia. Most writers have been obsessed, from time to time, by particular dangers, for example the dangers of cocaine toxicity, of explosion or of reducing the diameter of the airway. The desire to avoid one or other of these dangers has often led to the use of complicated equipment and extravagant combinations of drugs, some of which are themselves potentially unsafe. The explosion hazard affords such an excellent illustration of this tendency that the report of the Ministry of Health Working Party (1956) is worth quoting:

> It is important to note that the problem presented by the use of electrical apparatus in the theatre and elsewhere is not all told in the histories of anaesthetic explosions. There are also the misadventures which occur because the anaesthetist is afraid to use an explosive anaesthetic in conjunction with such apparatus. It is usual to wish to avoid the use of explosive anaesthetics in the X-ray room, and generally there is no difficulty in finding a nonexplosive alternative. There are, however, a few procedures, all of them quite short, for which the only wholly satisfactory anaesthetic is ether, and at present students are often taught to avoid ether and use some other drug which is medically unsuitable so as to avoid any risk of explosion. In our view the risk of an explosion in a modern X-ray room is easy to exaggerate: in particular we consider that the risk of a dangerous explosion where the patient is anaesthetized with open ether in the anaesthetic room and brought in unconscious is negligible.

There are other problems as well as safety, most of which are hardly mentioned by the majority of authors. Every technique has its advantages and disadvantages and there are often particular points which, although small in themselves make a vast difference to the number of successes. Nobody is competent to judge any method in these respects except a person who has had a great deal of experience with it, yet the anaesthetists who have devised and used the various methods outlined above have never thought fit to discuss these matters. Several writers have claimed as an advantage of their technique that alveolar filling does not occur, but none has studied the influence of alveolar filling on the acceptability of the films nor mentioned whether their surgeons and physicians prefer an underfilled bronchogram to an overfilled one. It is often mentioned that the patient is postured, and some detailed descriptions of the procedure are given, but these procedures are often copied from one source to the next and no author claims to have made a study of which method of posturing is best suited to his method of anaesthesia. Sometimes the child is positioned before the dye is introduced and sometimes the injection is completed and the mask replaced before the child is turned to one side. The present author has watched the entry of dionosyl into the bronchial tree under open ether fluoroscopically: with this particular form of anaesthetic it requires only three or four good breaths to fill all the main segmental bronchi of both lungs, and in a child this is a very short time indeed. Posturing, therefore, if it is to be of any value whatsoever must be extremely rapid, but whether the same considerations apply to other forms of anaesthesia seems to be largely a matter of guesswork. Furthermore, it requires only the most superficial knowledge of the nature of bronchography and the conditions for which it is employed to realize that it is quite impossible for every bronchogram to be acceptable, and yet not one writer has mentioned a single failure. Each anaesthetist tells us that his method is "satisfactory", and we must accept his word that it is, but it would have been of enormous benefit to many clinicians and radiologists if the results had been analyzed and the causes of failure discussed. The only exception to the above remarks is the Brompton Hospital series of cases, published by Bates et al. (1951). They discussed the results of a method using a cyclopropane induction followed by endotracheal nitrous oxide-oxygen-ether. The criteria of acceptability of the bronchograms were enumerated, and the percentage of satisfactory films was given. The oil was introduced through a catheter and careful posturing was carried out. In an addendum to the article a case was described of vagal inhibition, resulting in permanent decerebrate rigidity.

In the following pages an attempt will be made to evaluate the results of one particular method

of bronchography as practised by one particular group of anaesthetists attempting to satisfy the specific requirements of their own team of physicians and surgeons. Very little more than this will be attempted since there is not sufficient information available at the moment for a statistical comparison with any other method.

PRINCIPLES OF THE METHOD

(a) *Preparation.* Most of the patients have bronchiectasis and preradiological postural drainage is essential. It is impossible to be certain that a child is ready for bronchography by studying the quantity of sputum; some of the "driest" children have tenacious sputum firmly lodged in the affected segments, which are therefore unfillable, and some of the "wettest" have loose secretion in the larger bronchi only. Two weeks of postural drainage should be allowed for most cases; in the absence of acute infection there is little point in waiting more than three. A good ward sister will personally supervise the thoroughness of postural drainage and she is often the best judge of when the child is ready.

(b) *Premedication.* The desirability of an active cough reflex at the end of the procedure makes it advisable to use atropine alone. Children seem to be less nervous in the X-ray department than in the theatre and very little trouble is experienced. A child who is genuinely frightened should never have an anaesthetic forced on him, and if necessary the whole procedure should be postponed. A child who makes a fuss because previous experience has led him to believe that it will get him out of something he has decided not to like is better handled firmly.

(c) *Induction.* If a rapid induction can be achieved the high initial concentration of ether in the cerebral circulation will give a long enough period of anaesthesia for taking the films, after which the child will awaken as a result of redistribution of the ether in the body. It is important to note that this waking does not depend on excretion of ether through the layer of dye that has been put on the bronchial walls, and so the vicious circle of slow induction and slow recovery is avoided. Once the child is light enough to cough he will clear his own airway of ether and dye. As a corollary to this, it is unreasonable to use any inhalation agent for induction in a child with copious secretion, since this is bound to be a slow process. In the present series induction was achieved with thiopentone, ethyl chloride or divinyl ether, according to the circumstances and the preference of the anaesthetist.

(d) *Maintenance and Radiology.* After induction open ether anaesthesia is used. The mask is taken off when the third plane of the third stage has been reached, and all ether is removed from the vicinity of the X-ray apparatus. The child is allowed to breathe air until anaesthesia just begins to lighten, the mouth is opened and the radio-opaque dye is poured quickly over the back of the tongue. The mouth is then closed and the lower jaw supported in the usual manner, any residual dye being wiped from the lips with gamgee. Twenty ml dye are used in most cases but in larger children and those with grossly dilated bronchi 30 ml may be required. As soon as the anaesthetist hears inhalation of the dye beginning a cassette is placed under the chest and an anteroposterior (a.p.) film is taken; by the time this is exposed five or six breaths will have occurred. Right and left oblique films are then taken, in either order, as quickly as possible, followed by a second a.p. film. Apart from turning the patient into position for the oblique films no attempt is made at posturing, the object being to fill all segments of both lungs by means of the patient's spontaneous respiratory movements. In this way the nearest possible approach is obtained to the child's natural breathing state, and from the appearance of the films it is possible to form some idea of the functional as well as the anatomical extent of his disease (plate 1).

As soon as the films have been taken the trolley is wheeled up and the child is laid across it, prone, with his legs hanging over one side and his head supported by the nurse, over the other. A pillow is placed under the abdomen. In this position the back of the chest can be percussed; the child soon begins to cough, and may vomit. Although both oxygen and suction should be available, severe cyanosis is rare and suction is hardly ever required. When active reflexes are present and most of the dye has been coughed out the child may safely be returned to the ward

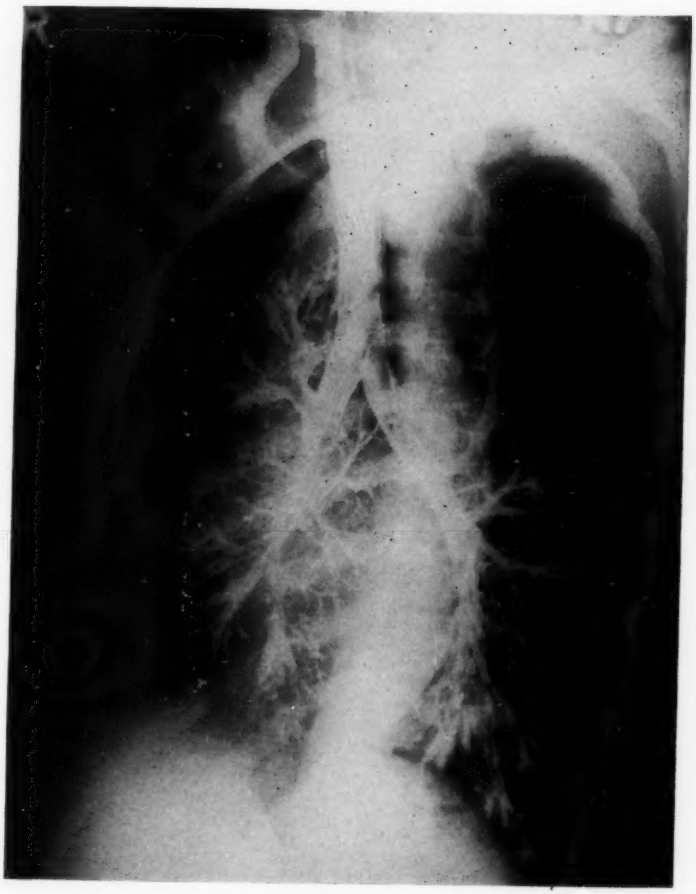

PLATE 1

Girl aged 12. History of primary complex with typical shadow of a collapsed middle lobe on straight X-ray five years previously. Oblique film correctly positioned to show right side; perfectly even distribution of dye with no sign of the middle lobe whatsoever. This film was not accepted: bronchoscopy revealed no secretion in the middle lobe opening and a repeat bronchogram with an endotracheal method after bronchoscopic suction still did not fill the middle lobe. At operation it was grossly diseased and solid.

lying on his side. In every case vigorous coughing occurs before the patient leaves the X-ray department (plates 5a and 5b).

REVIEW OF CASES

In order to include all the patients who had a bronchogram under open ether the records of the Liverpool Thoracic Surgical Unit at Broadgreen Hospital were traced back to January 1, 1945. Between January 1, 1945, and September 30, 1956, 472 patients had one or more bronchograms under general anaesthesia at some time. The total number of bronchograms relating to these patients was 763, the distribution according to method being as in table I.

The first open ether bronchogram, without bronchoscopy, was performed in 1947, all the remaining 501 being between 1948 and 1956. The rise in popularity of the method is shown in table II.

The X-rays and case sheets provided enough information to assess the quality of the bronchograms in 460 of the 502 open ether cases. Of these 460, 328 were accepted at the first attempt, giving a crude success rate of 71.4 per cent. The patients were anaesthetized by 23 different anaesthetists and a variety of radio-opaque substances was used; for these and other reasons the whole series is not sufficiently well controlled for the success rate to be of any great significance. It is, however, possible to study the influence of various factors on the success rate from the series as a whole, and after this has been done the last 100 cases will be discussed separately since these constitute a standardized series in themselves.

TABLE I

Open ether		502
Following bronchoscopy:		
under nitrous oxide-oxygen trichloroethylene, etc.	74	
with muscle relaxant technique ...	44	
		118
Muscle relaxant technique (without bronchoscopy)		13
Nitrous oxide-oxygen with ether or trichloroethylene		8
Local anaesthesia		109
Method in doubt		13
		763

TABLE II

Year	1945	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955	1956	Total
No. open ether bronchograms	0	0	1	56	69	62	33	55	35	70	60	61	502
Others	54	37	30	39	18	19	6	16	10	8	11	13	261
Total	54	37	31	95	87	81	39	71	45	78	71	74	763
Open ethers as percentage of total	0	0	3.2	59.0	79.3	76.5	84.7	77.5	77.9	89.6	84.5	82.5	

TABLE III

Year	Total number of open ether bronchograms of known quality	Number accepted at first attempt	Per cent
1948	50	30	60.0
1949	61	46	75.5
1950	49	32	65.4
1951	31	23	74.3
1952	48	34	70.9
1953	34	22	64.8
1954	68	45	66.2
1955	58	49	84.5
1956 (to Sept. 30)	60	46	76.4
Total	459	327	71.2

PLATE 2a

Residual bronchiectasis after right middle and lower lobectomy. Film taken in expiration.

PLATE 2b

Same case as plate 2a. More filling has taken place and a little oil has entered the stomach. This film was in inspiration, as evidenced in this emphysematous child by the more horizontal position of the ribs and the flattening and slight descent of the diaphragm. The change in diameter of the bronchi is striking; the lumina have opened up and the oil now lines the walls.

Influence of Various Factors on the Success Rate.

(i) *Presence of structural disease.* Forty-four of the present cases had anatomically normal bronchial trees and in only two of these was the bronchogram not accepted first time, giving a success rate of 95.5 per cent compared with 71.4 per cent in the series as a whole. Both the failures were in bronchitic children with copious sputum, the significance of which is further discussed below.

(ii) *Presence of sputum.* There was obvious evidence of secretion in the bronchial tree in 122 cases (26.5 per cent), presenting the usual appearances of "stops" and "branches cassées" (Huizinga and Smelt, 1950; plate 3). In some of these cases it was noted in the records that

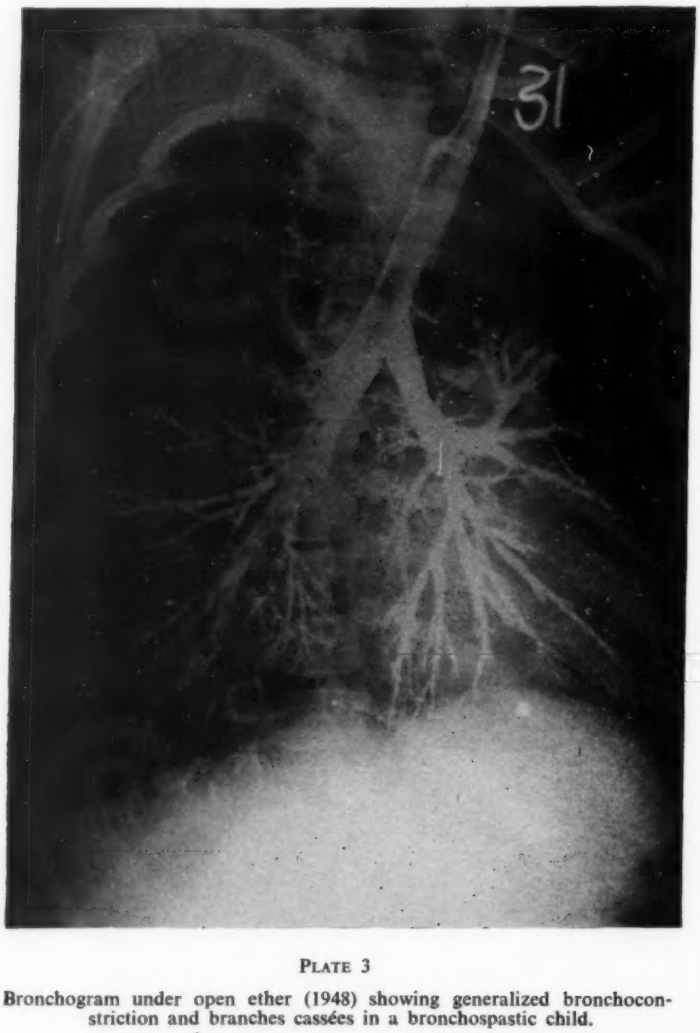

PLATE 3

Bronchogram under open ether (1948) showing generalized bronchoconstriction and branches cassées in a bronchospastic child.

abundant sputum was present, but it must be stressed again that the important factor in obtaining good bronchograms is not the quantity of sputum coughed up but the quantity left behind. The fact that only 26.5 per cent of the cases had residual secretion speaks well for the pre-operative management. Eighty-two of these 122 bronchograms were accepted (67.3 per cent), indicating that the presence of secretion is not invariably significant.

(iii) *Experience with the technique.* There was no progressive increase in the percentage of bronchograms accepted each year (table III), suggesting that the cumulative experience of the several anaesthetists had little influence on the results.

(iv) *Experience of the anaesthetist.* Two of the anaesthetists involved in the series had numbers of cases suitable for investigating the effect of increasing experience on the results obtained.

(*a*) One anaesthetist carried out bronchography throughout the whole of two consecutive years, using lipiodol for all cases, with results as in table IV.

TABLE IV

Year	Number of bronchograms	Number accepted	Per cent
1948	17	14	82.4
1949	22	17	77.3

(*b*) In a second series 100 bronchographies of known quality were performed in 15 months. A comparison was made (table V) of the first 6 months (July–December) with the last 6 months (April–September).

TABLE V

	Number of bronchograms	Number accepted	per cent
First 6 months	39	34	87.3
Last 6 months	43	35	81.5

In this series there were 6 patients in the first 6 months with normal bronchial trees (15.4 per cent) and 8 in the last 6 months (18.6 per cent) so that this factor would not influence the relative success rates. Dionosyl was used throughout.

There is no evidence of learning from experience either from one anaesthetist to the next or in the case of individual anaesthetists, which is perhaps to be expected with such an inherently simple technique. It is for this reason that the method is of such value to the anaesthetist who is only called upon to perform an occasional bronchogram.

(v) *Age of the patient.* All the open ether cases were children, and the results were equally good in all the age groups encountered (table VI).

TABLE VI

Age of patient (years)	Number of bronchograms	Number accepted	Per cent
1–2	7	5	71.5
3–4	16	12	75.0
5–6	110	78	70.9
7–8	158	114	72.2
9–10	96	71	74.0
11–12	55	35	63.7
13 and over	18	13	72.3
Total	460	328	71.4

(vi) *Anaesthetist.* Most of the 23 anaesthetists had relatively few cases, the great majority of the bronchograms being performed by six successive senior registrars. These six sets of results are presented in table VII.

TABLE VII

Series	Number of bronchograms (excluding normal bronchial trees)	Number accepted	Per cent
A	48	36	75.0
B	54	32	59.3
C	44	30	68.2
D	54	31	57.4
E	27	21	77.4
F	82	61	74.4

Although such a degree of variation is, statistically, quite liable to occur by chance, it does seem in practice that some anaesthetists are rather more successful than others.

(vii) *Premedication.* Following Temple and Gray, most anaesthetists kept to atropine alone except in occasional cases. The actual premedication used is often not ascertainable, but within

the range and dosage likely to have been employed it would not affect the results.

(viii) *Climate.* Many bronchiectatic children are at their worst in the winter and find their sputum most difficult to void at this time. Also, any lowering of the temperature of the radio-opaque substance will render it more viscous. Both these factors will make for a high failure rate in the winter and should lead to a reduced incidence of alveolar filling at this time. In fact these effects are not seen, probably because the changes in internal temperature in an X-ray department are comparatively small, and because some of the more bronchitic children are not admitted for bronchography until the weather improves. The actual figures are given in table VIII. It should be noted that the months January–April show both the lowest success rate and the lowest total number of bronchograms, suggesting that these are the worst months and that some of the worst cases were postponed.

(ix) *Radio-opaque substance.* The records of which substance was used for each bronchogram are incomplete, but it is known that since its

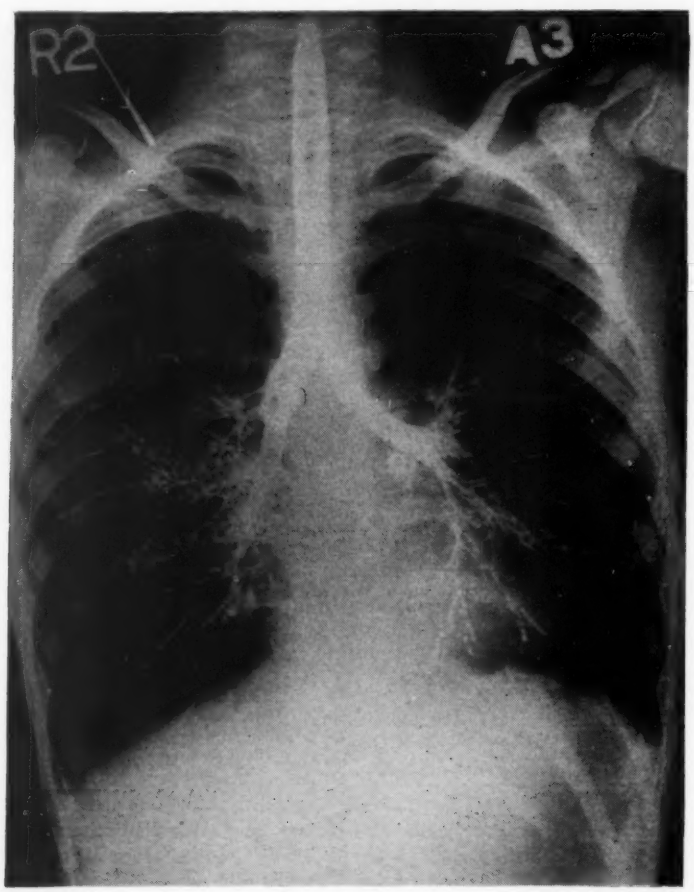

PLATE 4
Congenital microbronchi shown under open ether.

TABLE VIII

		Number accepted	Per cent	Overfilled (alveolar)	Per cent	Underfilled (see below)	Per cent
Total number of bronchograms in 1st quarter of every year 1948–56 inclusive	101	69	68.4	43	42.5	20	19.0
do. 2nd quarters	105	77	76.2	46	43.8	19	18.1
do. 3rd quarters	126	89	70.7	46	36.5	38	36.2
do. 4th quarters 1948–55 inclusive	126	91	72.3	54	42.8	36	31.4
	458*	326*		189*		113	

* One bronchogram for 1955 is not included since it is not known which quarter it comes into. It was accepted and showed alveolar filling.

introduction in February 1953, dionosyl has been used exclusively. The overall yearly success rates show no dramatic change with this innovation (table III), but the incidence of alveolar filling declined significantly (fig. 1; table IX).

TABLE IX

Year	Per cent bronchograms with alveolar filling
1948	50
1949	48
1950	53
1951	39
1952	60
1953	53
1954	26
1955	31
1956	23

Imperfections.

These may be grouped in the following way:

(*a*) Attempt abandoned.
(*b*) Failure of X-ray apparatus.
(*c*) Overfilling (alveolar filling).
(*d*) Underfilling
  (i) generalized
  (ii) of particular segments or lobes.
(*e*) Oesophageal filling.

(*a*) *Attempt abandoned.* Two attempts were abandoned before any dye had been introduced, in each case because of excessive sputum. The first case, in 1948, was repeated with a relaxant technique and fairly satisfactory films were obtained showing a cystic lower lobe. The second, in 1956, had a repeat bronchogram under nitrous oxide-oxygen-ether preceded by bronchoscopy and suction, which was accepted as a normal bronchial tree (vide supra).

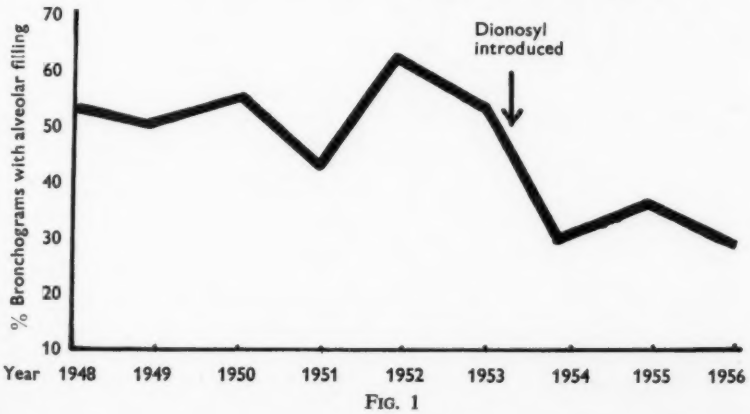

FIG. 1

(*b*) *Failure of X-ray apparatus.* This happened only once in twelve years. One a.p. film was obtained and this was not accepted.

(*c*) *Overfilling.* Some degree of alveolar filling was noted in 190 cases (41.2 per cent), most commonly as a gravitational effect in the dorsal segments of the lungs. Only very occasionally was it noted that the presence of alveolar filling made the X-rays difficult to interpret; as a rule a well filled picture (the "arbre en été" of continental writers) was much preferred to an underfilled one. One hundred and fifty-one of the films with alveolar filling were accepted (79 per cent, compared with 71.4 per cent in the series as a whole).

(*d*) *Underfilling.* These cases are classified in the following way:

(i) Generalized:

No peripheral filling, i.e. "arbre en hiver", one side or both sides.

Poor peripheral filling, i.e. "arbre en printemps", one side or both sides.

One side underfilled, i.e. whole of left or right lung.

Both sides underfilled, i.e., stem bronchi only, or less.

(ii) Specific lobes or segments not adequately filled.

The incidence and failure rates of these various shortcomings are shown in tables X and XI.

As would be expected, the films with stem bronchi or less were usually quite unacceptable (18.9 per cent accepted) whereas many of the films with poor or no peripheral filling were adequate for the surgeons' needs (58.4 per cent accepted).

Both upper and lower lobes show greater difficulty in filling on the left side than the right, no doubt because of the better anatomical alignment of the right main bronchus with the trachea and its larger diameter. The lingula and middle lobe both show relatively a very high incidence of underfilling, due to two factors: (i) their ventral position, which means that in the supine position the dye has to be aspirated into them against gravity, and (ii) the commonness of disease in these areas during childhood.

TABLE X

	Total number	Number accepted
Poor or no peripheral filling	65	38
Left side underfilled	7	2
Right side underfilled	3	1
Stem bronchi or less	38	6
Total	113	47

TABLE XI

	Total number	Number accepted
Left side:		
Upper lobe	11	4
Lower lobe	16	7
Lingula	16	8
	— 43	— 19
Right side:		
Upper lobe	5	1
Lower lobe	11	2
Middle lobe	23	11
	— 39	— 14
	82	33

(*e*) *Oesophageal filling.* Some outlining of the oesophagus was seen in 43 cases (9.3 per cent), and 26 of these cases were accepted (60.5 per cent). The rather low rate of success is due not so much to any direct consequence of oesophageal filling as to the fact that the more dye enters the oesophagus the less is left to fill the bronchial tree.

Complications.

There was no mortality in the series and no significant morbidity. One child had an exacerbation of bronchitic symptoms, with pyrexia, the day after bronchography; this was an ill child who had frequent attacks of this kind.

Routine iodine sensitivity tests were not performed, and no immediate or delayed reactions were noted. In at least one case a bronchogram was successfully carried out, using dionosyl, in a child stated to be sensitive to iodine, no previous desensitization having been attempted. The delayed complications of bronchography were discussed by Robertson and Morle (1951), having previously been described by Kooperstein and Bass (1946) and Bass (1949). Prompt removal of the radio-opaque substance by means of postural drainage protects against these complications (Lichter, 1951) and the efficacy of the present

PLATE 5a

Bronchogram 11 a.m. Gross disease of right lung.

PLATE 5b

Same case as plate 5a. Straight film 3 p.m. showing efficacy of postural drainage in emptying large cavities.

technique in this respect is illustrated by plates 5a and 5b.

STANDARDIZED SERIES OF CASES

In the fifteen-month period from July 1955 to September 1956 the author performed a total of 102 bronchograms under open ether. There is insufficient information available in two cases to make a fair assessment of the films and the subjoined data refer to the remaining 100 cases.

The conditions were standardized in every possible respect. All the films were taken in the same room, with the assistance of the same radiographers. The same posture was used, as described above, for every case except one in which the dye was introduced in the semilateral position with the deliberate intention of producing a unilateral bronchogram. Dionosyl oily 60 per cent was used in every case, at room temperature and after vigorous shaking of the bottle. The same premedication of atropine alone was used throughout. In every case except one the anaesthetic sequence was thiopentone, ethyl chloride, open ether; the exception was a child of eighteen months in whom thiopentone was not used. This anaesthetic sequence has the advantage of producing a rapid induction by means of an agent which does not depend for its effect, or its excretion, on the state of the lungs. By the judicious use of ethyl chloride the dosage of thiopentone can be kept to a minimum and the patient can be persuaded to accept the ether very rapidly. Laryngospasm does not occur (Lee, 1953).

Results.

Out of 100 cases, alveolar filling of some degree was present in 27, and poor or no peripheral filling in 23. Eight cases showed stem bronchi or less. Secretion was noted in 26 cases and dye was present in the oesophagus in 7. There were 16 cases with anatomically normal bronchial trees, of which 14 (87.6 per cent) had an acceptable bronchogram. Difficulty in filling particular lobes was encountered in 24 cases (table XII).

TABLE XII

Upper lobes	1 case
Lower lobes	12 cases
Lingula	3 cases
Middle lobe	8 cases

Eighty bronchograms were specifically noted as being acceptable, and in one further case an unaccepted bronchogram was vindicated by subsequent operative findings, the minimum success rate thus being 81 per cent. One of these bronchograms, however, was accepted only because the lingula had been seen on a previous film.

There were 92 patients in the series, of whom 76 had a bronchogram stated to be satisfactory at the first attempt (82.6 per cent) and another 5 had a bronchogram accepted after two attempts. This means that after two bronchographies satisfactory films were obtained of both lungs in 88.1 per cent of patients, which must compare favourably with any method designed to fill only one lung at a time. Two patients had a second failure with open ether; in one of these an alternative method gave better films, in the other case a satisfactory surgical decision was made on the combined evidence of the two bronchograms and a subsequent, postoperative bronchogram with open ether was accepted at the first attempt (this patient is included in both groups).

Ten patients had an unsatisfactory bronchogram which was not repeated under ether. Four of these were repeated with a different method, two had some doubt about the middle lobe which was resolved by bronchoscopy, one was accepted on the strength of a previous film, and in one a doubtful judgment was upheld at operation. The remaining two were actually accepted, with some reserve, although admittedly not entirely satisfactory. After two attempts with the open ether method, therefore, 94.6 per cent of the patients required no further bronchography. The fate of these 92 patients is summarized in table XIII.

TABLE XIII

Satisfactory at first attempt	76
Not completely satisfactory, but accepted ...	2
Accepted on strength of previous film plus present film	1
Doubtful judgement upheld at operation ...	1
Diagnosis established by bronchoscopy	2
	82
Repeated by alternative method after only one ether	4
Satisfactory at second attempt with ether ...	5
Repeated by alternative method after two ethers	1
	92

CONCLUSION

These bronchograms have been assessed on the criterion of acceptability, which is by no means always synonymous with complete filling. It has been shown that an anatomically normal bronchial tree is easier to fill than one which is distorted or in part dilated, but this is no more than would be expected. With abnormal bronchial trees one is often prepared to see incomplete filling for a variety of reasons. In the case of tuberculous hilar adenitis, for example, the purpose of bronchography may be to demonstrate that the middle lobe does not fill, and almost half the cases with no filling of the middle lobe were accepted first time (table XI). The same high rate of acceptance is seen in the case of underfilled lingulae (table XI), presumably because the association of lingular bronchiectasis with changes in the left basal segments is so common that in the presence of the latter an underfilled lingula can be taken as diseased until proved otherwise. In any event the bronchogram is unlikely to be rejected on this account since in the presence of an operable lesion of the left lower lobe it is easy to assess the condition of the lingula at thoracotomy. It must also be remembered that even when there is no anatomical or structural abnormality of the bronchial tree the patient may have a productive cough, and the presence of copious sputum constitutes a functional abnormality giving rise to just as much difficulty, from the bronchographic point of view, as frank bronchiectasis. In these cases repetition of the bronchogram is frequently required not only in order to establish the anatomical normality of divisions not previously outlined because of secretion, but also to find out whether these divisions remain normal with the passage of time.

When a part of the bronchial tree fails to fill, two questions arise: firstly, is the obstruction temporary or permanent; secondly, are the bronchi distal to the obstruction anatomically normal. Postural drainage and chemotherapy can do a great deal towards eliminating sputum as a cause of temporary obstructions, but in some cases the sputum is so copious or so tenacious that it will always cause difficulty. Bronchoscopy and suction may help in these circumstances and may already have been performed—indeed a bronchogram is sometimes only accepted in the light of what has previously been ascertained by other means. On the other hand, there has been no convincing evidence from Broadgreen that routine prebronchographic suction gives better results. Between 1945 and 1948 there were 86 cases treated by bronchoscopy and suction followed by direct instillation of lipiodol into the affected areas. All these were performed under general anaesthesia, with or without a muscle relaxant, and only 47 had an acceptable bronchogram (54.7 per cent). Over the whole twelve-year period of this review there were 12 patients in whom the open ether method gave a better bronchogram than local anaesthesia, 1 in whom it was superior to nitrous oxide-oxygen ether, and 1 in whom it was superior to bronchoscopy and suction. Local anaesthesia gave a better result than bronchoscopy and suction in 5 patients; it was superior to open ether in 4 and to a relaxant technique in 2. A relaxant technique proved better than open ether in 1 case, better than local anaesthesia in 2 cases and better than bronchoscopy and suction in 1. Bronchoscopy and suction improved on a relaxant technique in 3 cases and in only 2 cases did it give better films than a previous open ether.

It has been suggested (Lucas, 1952) that because of its bronchodilator action ether may produce misleading bronchograms. Structural disorganization of the bronchial wall is a feature of bronchiectasis and among its consequences are said to be loss of the power of bronchoconstriction in the affected areas and absence of the normal changes in diameter during respiration. It is theoretically possible that if the administration of ether were to cause a paralytic dilatation of the whole bronchial tree an important mark of distinction between normal and abnormal areas might be lost, and sufficient widening might be produced even to simulate bronchiectasis where none existed. On the other hand, it could be argued that minor changes are notoriously difficult to assess in any case, and that in the kind of lesion likely to be treated by surgery there is usually sufficient change in the shape as well as in the diameter of the bronchi to make a serious mistake extremely improbable.

In practice, prolonged ether anaesthesia may

lead to considerable bronchial relaxation but with the rapid induction used in the present series no diagnostic difficulty has been experienced. Plates 2a and 2b show how respiratory changes in bronchial calibre are preserved under ether even in the presence of gross disease. The absence of bronchodilatation in a wheezy, bronchospastic child is well illustrated by plate 3, and plate 4, an extreme example, shows that the characteristic appearance of congenital microbronchi is still immediately recognizable.

In discussing the open ether technique Mushin and Lake (1951) state that there is danger of carrying infection from the mouth into the lungs, and that filling of the upper lobes may be unsatisfactory. Both these are criticisms which were made of the original Verschluckmethode as practised under local anaesthesia, and it is true that satisfactory filling of the upper lobes was hardly ever obtained (Huizinga and Smelt, 1950). Under local anaesthesia, however, the patients were sitting up, and there is not the slightest evidence that under general anaesthesia in the supine position the upper lobes are harder to fill than any other part of the bronchial tree (tables XI and XII). With regard to infection, it is difficult to see why the method should be more exceptionable than any other.

The literature on bronchography in children is quite inadequate in respect of facts and figures, but the general impression is that each thoracic unit uses its own method, with which it is quite well satisfied. When this happens it often means that the results are good whatever technique is adopted, and in the case of bronchography this was suggested as long ago as 1927 (Miller and Eglee, 1927). In each centre the people responsible for bronchography come to know what is required by their particular surgeons and physicians and there is no doubt that standards vary in this respect. It is clear from the present review that the open ether method does not give uniformly excellent results in all cases but it is to some extent the purpose of bronchography to show up imperfections. The method recommends itself because of its safety and simplicity and because it represents the nearest possible approach to the "normal" respiratory function of the patient. The child lies on his back, breathing spontaneously, unintubated, and anaesthetized sufficiently to prevent coughing in response to the introduction of oil. Under these conditions bronchography can become a fascinating study not only of structural derangement but also of proportionate functional behaviour within the various lung segments. Furthermore, no specialized skill is required and a minimum of apparatus will suffice.

From the point of view of the anaesthetist it appears that the method of bronchography discussed in this paper is at least as satisfactory as any other method in current use for children. It must be left to the chest physicians, thoracic surgeons, radiologists and paediatricians to decide whether it is more likely to offer them a solution to their problems than any alternative technique.

ACKNOWLEDGMENTS

I was greatly helped in the personal series of cases reported above by Doctors Sonia Avlamis and Max Morides (Athens) and Doctor S. Liu (Mauritius), and also by the radiographers whose speed and efficiency contributed greatly to the successful results. I should also like to thank the staff of the Liverpool Thoracic Surgical Unit for their co-operation.

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SOME CHEMICAL AND PHYSICAL FACTORS IN THE DEVELOPMENT OF FLUOTHANE*

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My assignment tonight is to talk about the way in which chemistry and physics can help in the choice of compounds to be tested pharmacologically as candidate anaesthetics, and I shall illustrate this by reference to the work which led to the discovery of halothane (Fluothane). I shall suggest that of the properties which are wanted in an anaesthetic there are three which can be fairly closely related to chemical and physical properties. These are (1) absence of chemical toxicity, (2) absence of inflammability and explosive hazards, and (3) anaesthetic potency itself, and I shall show how one may attempt to design a molecule which will have these properties, and conclude with a general discussion of recent theories of relationships between molecular structure and anaesthetic potency, with especial reference to the work of Ferguson and of Mullins.

The first question we had to ask when, in 1951, we began thinking about searching for new anaesthetics was just what a good anaesthetic ought to do. We consulted anaesthetists and were a little taken aback by the answer. A good anaesthetic, we were told, should provide rapid and smooth induction not unpleasant to the patient with no irritation of the respiratory tract, good muscular relaxation, and rapid and easy control of the depth of anaesthesia, a good margin of safety, absence of sweating and of secretion from the mucosae, no increase in capillary bleeding, no cardiac irregularities or adverse effects on any organs, compatibility with adequate oxygen, controllable blood pressure, good recovery with absence of vomiting and nausea, stability over soda lime, and that it should be non-inflammable and nonexplosive—a formidable list. Of course, we understand that some anaesthetists prefer to have each physiological response under the control of a separate drug.

It might be thought that since the biological processes involved in anaesthesia are so little understood, it would be impossible to rationalize the selection of compounds to test as anaesthetics. This is not so. Of course, it is quite impossible to assess from chemical and physical properties whether a compound will be a practical anaesthetic; far less could one hope to predict that a compound would be superior to those already in use. The verdict of the pharmacologist and of the anaesthetist himself cannot be anticipated; but although one cannot predict how a compound will show up in the all important finer points of anaesthesia, one may, by following the leads which are available, increase the chance of success by selecting the most profitable area of search.

Let us take first the question of toxicity. One way of reducing the risk that a compound will prove toxic is to work with compounds which are chemically inert and therefore unlikely to become involved in metabolic chemistry. One group of compounds which possesses a high degree of chemical stability is that of the fluorinated paraffins, in which chlorine and bromine may also be present.

Table I shows the formulae of some of these compounds which are widely used as refrigerants

TABLE I

Some typical Arctons

CF_2HCl	Arcton 4
CF_2Cl_2	Arcton 6
$CFHCl_2$	Arcton 7
$CFCl_3$	Arcton 9
$CF_2Cl.CF_2Cl$	Arcton 33
$CF_3.CHBrCl$	Halothane (Fluothane)

* Lecture delivered to the Section of Anaesthetics, Manchester Medical Society, May 15; 1957.

and in aerosols. When manufactured by I.C.I. they are known under the trade name, Arcton. The first two in the table, Arcton 4 and Arcton 6, are used as refrigerants. Arcton 6, Arcton 9 and Arcton 33 are used as propellants in aerosols. Paint, shaving soap, insecticide or perfume is packed under pressure with these low boiling compounds. When pressure is released through a simple valve the mixture is ejected usually as a fine spray, the Arcton evaporates, leaving the other ingredient behind. Also in the table is the formula of halothane. In passing we might note that the second carbon atom of halothane has bonds with four different atoms and halothane should therefore exist in two optically active isomers. The commercial product should be the racemic mixture, but we do not know how to resolve it into the dextro- and laevorotatory forms.

The Arcton compounds owe their use as refrigerants and in aerosols largely to their volatility, low toxicity and noninflammability, properties which are desirable in an anaesthetic inhalant. The first to suggest that the Arcton type of compound might be used as anaesthetics appear to have been Booth and Bixby (1932) who tested $CFHCl_2$ and CF_2HCl on mice. Both compounds produced convulsions. It is unfortunate that compounds of the Arcton type which are gases at room temperature frequently produce convulsions, as one might hope to find among these low boiling compounds, an anaesthetic of sufficient power to permit its use with adequate oxygen but weak enough to serve some of the purposes to which nitrous oxide is put.

In 1946 Robbins tested forty-two compounds on mice and, with the more promising, on dogs (Robbins, 1946). He recommended four compounds for further tests but no clinical trials ensued. Robbins's results were of especial interest when examined in the light of Ferguson's (1939) work, as will later be described. They did not, however, suggest any particular compound not tested by Robbins as a potential practical anaesthetic.

I might mention here that one difficulty in assessing the reliability of reported tests of compounds as anaesthetics is doubt as to the degree of purity of the samples used, which is rarely indicated. One cannot be certain that when undesirable side effects are reported, they are due to the compound under test and not to some undetected impurity. But in the last few years very searching analytical techniques have come into use, notably the gas chromatograph and the mass spectrometer, and we would not consider a compound as suitable for test as an anaesthetic unless it were about 99.95 per cent pure.

Of course, application of these specialized techniques calls for the co-operation of specialists in analytical fields, and one cannot overstress the fact that the discovery and industrial development of even so simple a compound as halothane calls for the co-operation of very many skilled workers, chemists, engineers, physicists—quite apart from the work that is necessary on the biological side. The development of halothane has been very much a team effort.

We had at Widnes laboratory considerable experience in the specialized techniques for manufacturing the Arcton type of compound and in our desire to make further practical use of the special properties of these substances we decided to search among them and other fluorine containing compounds for an anaesthetic.

Now the chemical inertness of these compounds is a consequence of the strong chemical bond between carbon and fluorine as a result of which the fluorine atom is extremely unreactive. The inertness of fluorine is especially pronounced in compounds containing the groups CF_3- or $CF_2=$, which are not only very stable themselves but also stabilize links between adjacent carbon atoms and halogen. Thus in halothane the CF_3- group reduces the reactivity of the chlorine and bromine on the adjacent carbon atom. It seemed probable, therefore, that compounds containing the groups CF_3-, or $CF_2=$ would, because of their high chemical stability be unlikely to interfere chemically with body metabolism. They should therefore have low toxicity.

So we hoped to minimize chemical toxicity by synthesizing very stable molecules. There is, of course, the other type of toxicity which is produced, like general anaesthesia, not by a chemical, but by a physical mechanism, when an excessive concentration of the compound in the body produces undesirable and sometimes irreversible toxic symptoms. The ratio of this toxic concen-

tration to that concentration which produces satisfactory anaesthesia, which I believe you call margin of safety or anaesthetic index cannot be predicted. There is, however, evidence accumulating that, among compounds of the Arcton type, the margin of safety may be greater in polar compounds or in compounds containing hydrogen. By "polar compound" I mean a compound in which the distribution of electrons is asymmetrical, so that all parts of the molecule have not the same electrical charge. The possibility of electrostatic interaction with other molecules is then present.

We decided, in 1951, to concentrate in the first place on compounds containing the groups CF_3- or $CF_2=$ to obtain stability and, we hoped, absence of chemical toxicity. As for making compounds which were noninflamable and nonexplosive, we knew that if we kept the percentage of hydrogen in the molecule low, this requirement would be met.

I should perhaps interpolate here a remark about the photochemical stability of halothane. As you may know, unstabilized halothane evolves bromine when exposed for some days to bright light. This evolution of bromine is completely prevented by addition to Fluothane, before sale, of 0.01 per cent w/w of thymol. The thymol acts by mopping up the free radicals produced by light, which would otherwise lead to bromine evolution by a chain reaction. As an added precaution Fluothane is stored in brown bottles, but the thymol itself gives adequate protection.

The remaining problem was the choosing of compounds with adequate anaesthetic potency. It might be thought that this would be a difficult matter, but, in fact, it is not, thanks principally to the work of Ferguson (1939, 1951), who was responsible for initiating the search which led to the discovery of halothane. In this, his earlier work on the theory of narcosis proved of great value. I am using the term "narcosis" to denote the reversible inhibition of any biological function.

Ferguson's contribution to the theory of narcosis, and therefore of anaesthesia, was to point out that the significance of data on narcosis is much greater when the concentrations of the drugs administered are expressed on a thermodynamic scale rather than in more usual ways, for example as percentages by volume.

Let us see how this works out. Table II shows results obtained by Meyer and Hemmi (1935) in experiments in which mice were anaesthetized by the compounds listed. The first column of figures gives the volume percentage of these compounds which were sufficient to produce anaesthesia. You will observe that the figures vary from 0.5 to 100 per cent, that is by a factor of 200.

TABLE II
Anaesthesia of Mice

Substance	Anaesthetic concentration per cent by volume	Relative saturation for anaesthesia p_a/p_s
Nitrous oxide	100	0.01
Acetylene	65	0.01
Methyl ether	12	0.02
Methyl chloride	14	0.01
Ethylene oxide	5.8	0.02
Ethyl chloride	5.0	0.02
Ethyl ether	3.4	0.03
Methylal	2.8	0.03
Ethyl bromide	1.9	0.02
Dimethylacetal	1.9	0.05
Diethylformal	1.0	0.07
Dichloroethylene	0.95	0.02
Carbon disulphide	1.1	0.02
Chloroform	0.5	0.01

Data for Meyer and Hemmi (1935): table from Ferguson (1939).

In the second column of figures the concentrations producing anaesthesia are expressed, as sugested by Ferguson, as relative saturations, that is to say, as the ratio of the partial pressure producing anaesthesia (p_a) to the saturated vapour pressure of the compound at the temperature of the experiment (p_s). (This ratio, the relative saturation, when applied to water in the atmosphere gives the familiar relative humidity). You will notice that, when anaesthetic concentrations are expressed in this way, the range of the values is greatly reduced. In this case it is 0.01 to 0.07, a factor of 7, compared with a factor of 200 when volume percentages are used.

The calculation of the ratio p_a/p_s should be clear from tables III and IV which give results with the Arcton type of compound in anaesthesia of mice. These tables include the saturated vapour pressure of the anaesthetic at 20°C p_s (either deter-

termined experimentally or estimated from known vapour pressure curves of similar compounds) and the partial pressure for anaesthesia p_a calculated from observed percentage by volume anaesthetic concentrations. The pressure at which the experiment is conducted is assumed to be 760 mm Hg, so that the partial pressure for anaesthesia equals anaesthetic concentration per cent by volume × 760 ÷ 100. Variations from 20°C and 760 mm Hg likely to occur during normal atmospheric conditions would not affect significantly the values for p_a/p_s which are given to one significant figure only.

The ratio p_a/p_s, the relative saturation for anaesthesia, has a fundamental thermodynamic significance which I shall mention shortly, but first I shall give two more series of results in which anaesthetic concentrations are again expressed as gaseous volume percentages and also as relative saturations.

Table III gives some results obtained by Robbins. The range of concentrations in volume percentage is 0.4 to 25 but in relative saturations 0.03 to 0.08. Unpublished results of Raventós and Suckling, also with mice, are given in table IV. The figures for the last three compounds are of interest in that the relative saturations required to produce anaesthesia are greater than with the other compounds in table IV and the compounds in table III. This may probably be attributed to the absence of hydrogen in the three compounds with the consequent effect on polarity or hydrogen bonding. It seems in fact that absence of hydrogen tends to reduce anaesthetic potency—expressed on this relative saturation scale—but it has less effect on lethal concentration expressed on the

TABLE III
Anaesthesia of Mice

Substance	Boiling point	Vapour pressure at 20°C p_s mm Hg	Anaesthetic concentration per cent by volume	Partial pressure producing anaesthesia p_a mm Hg	Relative saturation for anaesthesia p_a/p_s
$CF_3.CHBr_2$	73	104	0.4	3	0.03
$CF_3.CH_2Cl$	6	1400	8.0	60	0.04
$CF_3.CH_2Br$	26	600	2.8	21	0.04
$CF_2.CHCl_2$	29	550	2.7	21	0.04
$CFCl_2.CH_3$	32	470	2.5	19	0.04
$CHF_2.CH_2Cl$	36	420	2.2	17	0.04
$CF_2Cl.CH_2Cl$	47	280	1.3	10	0.04
$CF_3.CH_2I$	55	200	1.3	10	0.05
$CHF_2.CH_2Br$	57	190	1.3	10	0.05
$CF_2Cl.CH_2Br$	68	130	0.8	6	0.05
$CF_2Cl.CH_3$	−10	2300	25	190	0.08

Anaesthetic concentrations by volume from Robbins (1946).

TABLE IV
Anaesthesia of Mice

Substance	Boiling point	Vapour pressure at 20°C p_s mm Hg	Anaesthetic concentration per cent by volume	Partial pressure producing anaesthesia p_a mm Hg	Relative saturation for anaesthesia p_a/p_s
$CF_3.CHBrCl$	50	243	0.9	7	0.03
$CF_2.CHBr_2$	73	104	0.6	5	0.05
$CF_2Cl.CHCl_2$	72	110	0.8	6	0.05
$CF_3.CHBr.CH_3$	49	260	2.2	17	0.07
$CF_2Br.CF_2Br$	46	290	4.1	31	0.11
$CF_3.CCl_3$	47	280	4.6	35	0.13
$CF_2Cl.CFCl_2$	48	270	5.6	43	0.16

same scale. (The figures for lethal concentrations are not shown in the table). This suggests that, in the class of compounds which we have studied, those containing no hydrogen will have a smaller margin of safety and a lower potency compared with similar compounds containing hydrogen.

The results in tables II and III suggest the tentative hypothesis that any compound which is not chemically toxic will probably produce anaesthesia, if administered at a relative saturation of 0.03 to 0.08. Such generalizations are, however, not strictly true (Ferguson, 1951) and I shall comment on some striking exceptions later. Nevertheless, this generalization holds as a rough rule for a surprisingly large number of compounds of relatively low molecular weight. The higher the boiling point of a compound the lower will be its saturated vapour pressure at any temperature. So we can get a good idea of how potent a compound will be as an anaesthetic from its boiling point.

While on the subject of boiling point I might mention that we do bear in mind the fact that compounds boiling below about 30°C will have the practical disadvantage of necessitating storage in cylinders under pressure. On the other hand compounds with too high a boiling point may be excreted too slowly and delay recovery.

To return to the main theme. For one looking for an anaesthetic, the principal advantage to be gained from Ferguson's work is not that one can calculate in advance the approximate anaesthetic potency of a compound, useful though this is. It is, I think, that Ferguson's treatment shows that a very large part of the difference between the anaesthetic potencies of compounds when measured on the usual volume percentage scale is due to differences in saturated vapour pressure at the operative temperature. When these are allowed for, by expressing results as relative saturations, a much more uniform picture emerges, which shows, however, a previously unsuspected fine structure. Study of the residual differences which make up this fine structure can lead, in fact has led, to a much better understanding of the problem. Some otherwise obscure correlations are illuminated by Ferguson's concepts. For example, it had been argued that the chlorine atom possessed some peculiar power of confering anaesthetic potency on a compound, and it had been suggested that this might be due to some special effect in the brain. But Ferguson's work shows clearly that chloroform is a much more powerful anaesthetic than methane because its vapour pressure (p_s) is always much lower than that of methane. Therefore, if anaesthesia is produced by both at the same relative saturation (p_a/p_s) a much lower partial pressure (p_a) of chloroform will suffice to produce anaesthesia than will be necessary with methane. Thus what was believed to be a peculiar property of the chlorine atom is brought into line with the behaviour of any group or atom which, when substituted for hydrogen in a molecule tends to raise the boiling point. Ferguson (1951) has made a preliminary exploration of the relation of chemical constitution to narcotic potency measured on the thermodynamic scale.

I have now told you of some of the chemical and physical background which we had to help us when we started the work which led to the discovery of halothane. Some of the compounds which we chose to test were chosen because they were readily available but halothane, which was at the time an unknown compound, was selected on the basis of the considerations which I have outlined and specially made for testing as an anaesthetic.

I should like in the short time left me to bring up to date the discussion of the relationships between physical properties and anaesthetic potency. First by saying a little more about Ferguson's work and then by alluding briefly to recent theories advanced by Mullins. I have time for no more than a very quick and therefore imprecise exposition. Those who wish to know more of the subject will find the papers by Ferguson and by Mullins (1954) well worth perusal.

Let us return first to the factor p_a/p_s, which has a more fundamental significance than I have so far explained. The factor p_a/p_s is approximately equal to the thermodynamic function known as "activity". Thermodynamic activities are always referred to an arbitrary standard state to which unit activity is assigned. In this paper the pure liquid is taken as the standard state with unit thermodynamic activity.

It is a fundamental property of thermodynamic

activity of a substance, one expression of which is, as I have explained, p_a/p_s the relative saturation, that it is equal in all phases in equilibrium. By equilibrium is meant a steady state in which the rate of loss of anaesthetic from the tissues is exactly balanced by the rate of uptake. It follows that, when an anaesthetic has become distributed in equilibrium between the inspired air and the body tissues, its thermodynamic activity will be p_a/p_s in all the body tissues. This helps to circumvent the difficulty, which often arises in biological work, that one can discuss the concentration of a drug only as it is in the ambient medium, in the inspired air for example, when one is most interested in concentrations in the tissues.

There is a major group of compounds which diverge from Ferguson's generalization in that they exhibit no anaesthetic power and no toxicity at any thermodynamic activity. These are the perfluoro compounds such as perfluoropentane. Mullins found that the saturated vapour of pentane C_5H_{12} anaesthetized mice in 15 minutes, whereas the saturated vapour of C_5F_{12} perfluoropentane, had no effect whatever after one hour. Similar observations have been published by Banks, Campbell and Rudge (1954).

An explanation for these facts is offered by Mullins (1954). Mullins correlates narcotic potency with the work required to replace a molecule in some biological tissue by a molecule of the narcotic. This work depends on the difference between the cohesive energy densities of the tissue and the narcotic. The cohesive energy density, as its name implies, is a measure of the forces holding a liquid together. Cohesive energy densities are dependent partly on molecular size which assumes great importance in Mullins's theories.

If two substances have very different cohesive energy densities, then much work will be required to replace a molecule of one by a molecule of the other. There will be a large heat of mixing. When an anaesthetic and brain tissue form a solution which is far from ideal, the concentration of anaesthetic in both air and brain which is necessary to produce anaesthesia will be much higher than would be expected on the Ferguson basis. Perfluorocarbons have very low cohesive energy densities compared with those of brain tissues, and, even when the inspired air is saturated, enough perfluorocarbon to cause physiological activity is not transferred to the brain.

Mullins suggests that the cohesive energy densities of the brain tissue affected by anaesthesia is lower than that of body tissue in general. Therefore a good anaesthetic should have a cohesive energy density such that it is more readily taken up by the brain than by other organs. In an anaesthetic, like chloroform, which is liable to affect adversely some of the organs of the body, the cohesive energy density is too high and this permits it to be absorbed too readily in tissues other than the brain with consequent undesirable side effects. Mullins suggested that since the low cohesive energy densities of fluorocarbons lead to physiological inactivity perhaps some fluorochloroparaffin (that is Arcton type of compound) might have a suitable cohesive energy density for anaesthesia and still be stable and noninflammable. This suggestion was not made until after the discovery of halothane, although Mullins did not know of it.

I indicated earlier how the anaesthetic potency of a molecule seems to be markedly affected by its polarity. It is unfortunately not possible at present to calculate the effect of polar interactions on cohesive energy densities. We cannot tell whether polarity will be shown, eventually, to be another factor operating by modifying thermodynamic properties and so fit into the general picture, or whether the wheel will make a full turn in that polar interactions, and perhaps hydrogen bonding, will be found to have a specific effect in the production of anaesthesia.

You will have noticed that nothing has been said as to what is the mechanism by which anaesthetics produce anaesthesia. The theories which we have been discussing do not tell much about this, only that the mechanism must be thermodynamically reversible and physical. One may ask, what of the future? The discovery of halothane has led to a revived interest in the Arcton type of compound: many more of them will, no doubt, be tested. Whether as a result, new compounds will find their way into clinical practice remains to be seen. We may, at least, confidently hope that the work will contribute to a better understanding of the mechanism of anaesthesia.

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CORRESPONDENCE

COMPARISON OF SEVEN INTRAVENOUS ANAESTHETIC AGENTS IN MAN

Sir,—Drs. Wyant, Dobkin and Aasheim, reporting (*Brit. J. Anaesth*, **29**, 194) a series of experiments on five volunteers with intravenous anaesthesia state: "Because of its more detrimental effects, especially on respiration, hexobarbitone cannot be recommended."

A great number of people would not agree with them on that point and it is noteworthy that Drs. Dobkin and Wyant, two months later in the *Canadian Anaesthetists Society Journal*, publishing the same experiments on the same volunteers enhanced by two more subjects state, "*Hexobarbital*: The mean period of apnoea with this drug was 7 seconds with the mean dose of 517 mg/M^2. There was virtually no depression of the respiration or the metabolic rate"; and they go on to state, "on the whole hexobarbital had far less effect on either respiration or haemodynamics than thiopental and thiamylal for the corresponding state"; and later on, "all drugs significantly depressed oxygen consumption except hexobarbital"; and finally, "venous pressure was also reduced by all the drugs by at least 15 per cent with the least changes observed with hexobarbital and buthalitone".

These latter findings are more in accord with my own observations (Ruddell, J. S. (1955), *Brit. med. J.*, **2**, 972) and others (Morley, A. H. (1955), *Brit. med. J.*, **2**, 1353; Blair Gould, R. (1956), *Brit. med. J.*, **1**, 48; Mushin, W. W. (1954), *Anaesthesia*, **9**, 234; Blair Gould, R. (1955), *Anaesthesia*, **10**, 91), and it would be interesting to know if hexobarbitone was the drug to which they were referring in your journal, and if it was, what the observations were on the last two subjects which so reversed their conclusions on the previous five.

J. SHEGOG RUDDELL,
Alberta, Canada

Brit. J. Anaesth. (1957), **29**, 473

THE BARBITURATES: CHEMICAL CONSTITUTION AND NOMENCLATURE

BY

JOHN B. LLOYD

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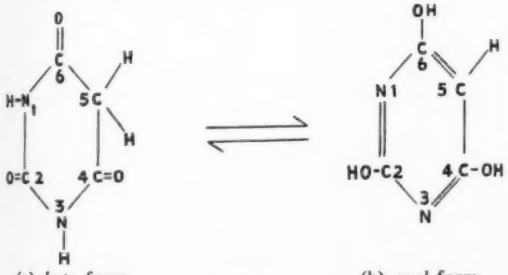
BARBITURIC acid was first synthesized by Conrad and Guthzeit in 1882, and in 1903 the 5:5-diethyl derivative was introduced into medicine as a hypnotic by Carl Fischer and von Mering, under the name of Veronal.

In the past, barbituric acid was usually regarded as the cyclic ureide of malonic acid, i.e. as malonyl urea, and its structural formula written in a form which emphasized this relationship. Systematically it is more correct to regard it as a pyrimidine derivative and to write its formula as shown in figure 1(a).



(a) *keto* form (b) *enol* form

FIG. 1
Barbituric acid

Barbituric acid is one of a group of compounds capable of existing in two forms, the "ketonic" and the "enolic". The structure shown in figure 1(a) does not account for its acidic properties, and the salts formed with the alkali metals are regarded as being derived from the enolic tautomer (fig. 1(b)) by replacement of one of the hydroxyl hydrogen atoms.

The barbiturates have provided a very fertile field for attempts to correlate chemical structure with pharmacological activity. The number of possible derivatives is practically limitless and very many have been prepared and submitted to investigation. As a result, certain principles have been formulated which make it possible to forecast the properties of any new derivative with some degree of precision. Nevertheless, there are still some unexplained exceptions. A well known instance is the compound 5-ethyl, 5-(1, 3-dimethylbutyl) barbituric acid described by Swanson (1934) which in spite of its similarity in structure to pentobarbitone is entirely devoid of hypnotic properties and purely convulsant in action.

The three principal methods for the production of variants are:

(*a*) substitution of the C^5 hydrogen atoms by organic radicles, e.g. diethyl barbituric acid.

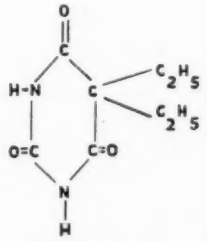


FIG. 2

(*b*) substitution of the N^1 hydrogen by an alkyl radical, e.g. methylphenobarbitone.

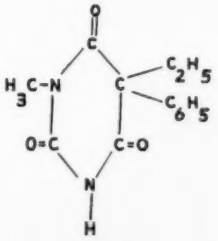
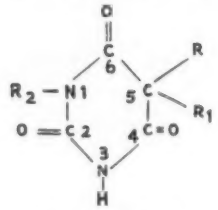


FIG. 3

TABLE I
Derivatives of barbituric acid



Generic Formula

Acid	Sodium salt	R	R_1	R_2	Duration of activity
BARBITONE, B.P. Barbital Malonal Veronal	BARBITONE SODIUM, B.P. Embinal Medinal Veronal Sodium	$-CH_2-CH_3$	$-CH_2-CH_3$	$-H$	Long
Metharbital, N.N.R. Gemonil	——	$-CH_2-CH_3$	$-CH_2-CH_3$	$-CH_3$	Anticonvulsant
——	Probarbital Sodium, N.N.R. Ipral Sodium	$-CH_2-CH_3$	$-CH(CH_3)(CH_3)$	$-H$	Medium
BUTOBARBITONE, B.P.C. Butobarbital Neonal Soneryl	Butobarbitone Sodium Soneryl Sodium	$-CH_2-CH_3$	$-CH_2-CH_2-CH_2-CH_3$	$-H$	Medium
——	Butabarbital Sodium, N.N.R. (Distinguish from Butobarbital) Butisol Sodium Noctinal (Sodium)	$-CH_2-CH_3$	$-CH(CH_3)-CH_2-CH_3$	$-H$	Medium
Aprobarbital, N.N.R. Alurate Isonal	Aprobarbital Sodium, N.N.R.	$-CH_2-CH=CH_2$	$-CH(CH_3)(CH_3)$	$-H$	Medium
——	Narconumal (Sodium)	$-CH_2-CH=CH_2$	$-CH(CH_3)(CH_3)$	$-CH_3$	Short

TABLE I *continued*

Acid	Sodium salt	R	R_1	R_2	Duration of activity

TABLE I *continued*

Acid	Sodium salt	R	R_1	R_2	Duration of activity
Noctal Noctenal Nostal	——	$-CH_2-C(Br)=CH_2$	$-CH(CH_3)_2$	—H	Medium
——	Eunarcon (Sodium)	$-CH_2-C(Br)=CH_2$	$-CH(CH_3)_2$	$-CH_3$	Short
ALLOBARBITONE, B.P.C. Barballyl Barbidal Curral Dial	——	$-CH_2-CH=CH_2$	$-CH_2-CH=CH_2$	—H	Medium
AMYLOBARBITONE, B.P.C. Amobarbital, U.S.P. Amytal	AMYLOBARBITONE SODIUM, B.P.C. Amobarbital Sodium, U.S.P. Sodium Amytal	$-CH_2-CH_3$	$-CH_2-CH_2-CH(CH_3)(CH_3)$	—H	Medium
PENTOBARBITONE, B.P. Pentobarbital, N.N.R.	PENTOBARBITONE SODIUM, B.P. Pentobarbital Sodium, U.S.P. Dorminal (Sodium) Nembutal (Sodium)	$-CH_2-CH_3$	$-CH(CH_3)-CH_2-CH_2-CH_3$	—H	Short
——	Vinbarbital Sodium, N.N.R. Delvinal Sodium	$-CH_2-CH_3$	$-C(CH_3)=CH-CH_2-CH_3$	—H	Short
Sandoptal	——	$-CH_2-CH=CH_2$	$-CH_2-CH(CH_3)(CH_2)$	—H	Medium
Butalbital Lotusate Talbutal	——	$-CH_2-CH=CH_2$	$-CH(CH_3)-CH_2-CH_3$	—H	Short
Pernocton Pernoston	——	$-CH_2-C(Br)=CH_2$	$-CH(CH_3)-CH_2-CH_3$	—H	Short
—— ——	Hexethal Sodium, N.N.R. Hebaral Sodium Ortal Sodium	$-CH_2-CH_3$	$-CH_2-CH_2-CH_2-CH(CH_2-CH_3)$	—H	Short

TABLE I *continued*

Acid	Sodium salt	R	R_1	R_2	Duration of activity
	QUINALBARBITONE SODIUM, B.P.		$-CH(CH_3)-CH_2-CH_2-CH_3$		
Quinalbarbitone Secobarbital, N.N.R. Seconal	Secobarbital Sodium, U.S.P. Evronal Sodium Seconal Sodium	$-CH_2-CH=CH_2$		—H	Short
Rectidon Sigmodal	——	$-CH_2-C(Br)=CH_2$	$-CH(CH_3)-CH_2-CH_2-CH_3$	—H	Short
Cylopal	——	$-CH_2-CH=CH_2$	$-CH$(cyclohexene-3-yl)	—H	Short
HEXOBARBITONE, B.P. Cyclonal Evipal Evipan Hexobarbital Methexenyl	HEXOBARBITONE SODIUM, B.P. Hexobarbital Sodium, N.N.R. Cyclonal Sodium Evipal Sodium Evipan Sodium Methexenyl Sodium	$-CH_3$	$-C$(cyclohexene-1-yl)	$-CH_3$	Short
CYCLOBARBITONE, B.P.C. Phanodorm Phanodorn	——	$-CH_2-CH_3$	$-C$(cyclohexene-1-yl)	—H	Short
Rutonal		$-CH_3$	$-C_6H_5$	—H	Anticonvulsant
PHENOBARBITONE, B.P. Phenobarbital, U.S.P. Gardenal Leonal Luminal Somonal	PHENOBARBITONE SODIUM, B.P. Phenobarbitone Sodium, U.S.P. Gardenal Sodium Luminal Sodium Phenobarbitone Soluble Somonal Sodium	$-CH_2-CH_3$	$-C_6H_5$	—H	Long
METHYLPHENOBARBITONE, B.P. Mephobarbital, N.N.R. Mebaral Phemitone Prominal	——	$-CH_2-CH_3$	$-C_6H_5$	$-CH_3$	Anticonvulsant
Heptabarbital, N.N.R. Medomin	——	$-CH_2-CH_3$	$-C$(cyclohexene-1-yl)	—H	Short

Methi
Nerva
Thiog

THAL
Kemi

Thiam
Surita
Thiose

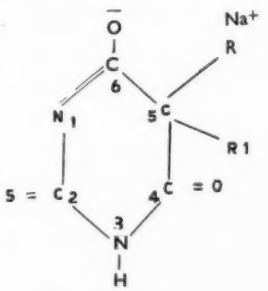
BUTTHA
Bayter
Transi
Ulbret

Thioet
Venesa

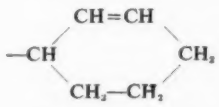
THIOPI
Thiope
Intrav
Pentot

TABLE II

Thiobarbituric acid derivatives (sodium salts)



Generic Formula

Sodium salt	R	R_1	Sulphur analogue of	Duration of activity
THIOPENTONE SODIUM, B.P. Thiopental Sodium, U.S.P. Intraval Sodium Pentothal (Sodium)	$-CH_2-CH_3$	$-CH(CH_3)-CH_2-CH_2-CH_3$	Pentobarbitone	Ultra short
Thioethamyl Sodium Venesetic (Sodium)	$-CH_2-CH_3$	$-CH_2-CH_2-CH(CH_3)_2$	Amylobarbitone	Ultra short
BUTHALITONE SODIUM, A.N. Baytenal (Sodium) Transithal (Sodium) Ulbreval (Sodium)	$-CH_2-CH=CH_2$	$-CH_2-CH(CH_3)_2$	Sandoptal	Ultra short
Thiamylal Sodium, N.N.R. Surital Sodium Thioseconal Sodium	$-CH_2-CH=CH_2$	$-CH(CH_3)-CH_2-CH_2-CH_3$	Quinalbarbitone	Ultra short
THIALBARBITONE SODIUM, A.N. Kemithal (Sodium)	$-CH_2-CH=CH_2$		——	Ultra short
Methitural Sodium Neraval (Sodium) Thiogenal (Sodium)	$-CH_2-CH_2-S-CH_3$	$-CH(CH_3)-CH_2-CH_2-CH_3$	——	Ultra short

(*c*) replacement of the C^2 oxygen by sulphur, e.g. thiopentone.

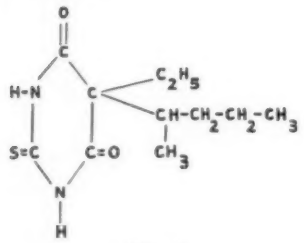


FIG. 4

Most of the earlier componds resulted from substitution at C^5. Barbituric acid itself, and its mono-alkyl derivatives are without measurable hypnotic activity. When both C^5 hydrogen atoms are substituted by alkyl groups, activity appears when the total number of carbon atoms in the substituent groups reaches four. A peak is reached at seven or eight, after which activity tends to decline with further increases. Bromination of one of the substituent alkyl groups enhances activity. Compounds with branched chain substituents usually show greater activity and longer duration of action than the isomeric straight chain compounds. Substitution at C^5 by two aromatic groups yields inactive compounds, but providing that one of the substituents is an open chain group the other may be cyclic.

Substitution at N^1 by methyl results in increased activity and shortened duration of action. Enhanced anticonvulsant properties have also been claimed. Higher alkyl groups exert the opposite effect and produce convulsant compounds.

Replacement of the C^2 oxygen by sulphur to form thiobarbiturates increases solubility in lipids and results in compounds characterized by an extremely short duration of action.

Barbituric acid and its derivatives are weak acids insoluble in water but form water soluble salts with the alkali metals. Solutions of the sodium salts are highly alkaline and decompose on keeping. Both the free acids and sodium salts may be used for oral medication, but only the latter are suitable for intravenous injection. The thiobarbiturates, in the form of their sodium salts, find their principal use as intravenous anaesthetics. They are not suitable for oral administration because of their rather erratic absorption from the gastro-intestinal tract.

The study of structure-activity relationships, has resulted in the production of a very large number of compounds ranging in activity from barbitone with an average hypnotic dose of 0.5 g to pentobarbitone for which the corresponding dose is 0.1 g. Duration of effect ranges from 12 hours or more in the case of phenobarbitone to approximately 15 minutes for thiopentone. Tatum (1939) classified the barbiturates into long, medium, short and ultra short acting. The long acting group exert their effect over 8 to 12 hours and upwards, the medium acting over 6 to 8 hours, the short acting over 2 to 3 hours, and the ultra short acting over 15 minutes. Duration of activity is a property which is not subject to precise determination, but a classification on this basis serves as a rough guide for clinical purposes.

In tables I and II, the chemical structure of the more important compounds is illustrated, and their duration of activity noted. Many of them are available both as the free acid and the sodium salt, and this leads to some confusion in nomenclature. For instance, in Britain, thiopentone sodium is sold under the proprietary name of Pentothal, whilst in the U.S.A. it is known as Pentothal Sodium. The American usage avoids ambiguity and in the tables the word " sodium " has been added to the proprietary names of compounds which are sodium salts. An exception occurs in the case of Medinal which is the sodium salt of Veronal.

In naming the compounds the official non-proprietary names are printed in capitals, but apart from this, proprietary and non-proprietary names have not been distinguished. The term " official non-proprietary name " denotes the name used to distinguish the compound in the *British Pharmacopeia* 1953 (B.P.) or the *British Pharmaceutical Codex* 1954 (B.P.C.) Compounds described in the *United States Pharmacopeia XV*, or *New and Non-Official Remedies* 1957 are indicated by the suffix (U.S.P.) and (N.N.R.) respectively. A.N. indicates a nonproprietary name approved by the British Pharmacopeia Commission.

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ON CHLOROFORM AND OTHER ANÆSTHETICS

THEIR ACTION AND ADMINISTRATION

BY

JOHN SNOW, M.D.

Licentiate of the Royal College of Physicians

(*Continued from page* 432)

"*Case* 3. On the 6th of March, 1852, I had occasion to remove the finger of a robust, healthy-looking young man, in the Royal Infirmary. He was already under the influence of chloroform when I entered the room, and as there had been some difficulty in producing complete anæsthesia, and the last of the chloroform in the bottle was already on the handkerchief, it was thought advisable by my friend in charge of its administration to keep up the inhalation, in order to produce a coma sufficiently profound to last until the completion of the operation. It was therefore left over his face, and I commenced and removed the finger, slowly disarticulating it from the metacarpal bone. I distinctly recollect hearing the man breathing quickly and shortly; and I also remember, that when just about to look for the vessels, my attention was attracted to his condition, by not any longer hearing the respiration. The handkerchief was still on his face. I took it off, and found, to my consternation, that the breathing had ceased; the face was livid; the eyes suffused; the pupils dilated; the mouth half-open. He was to all appearance dead; still the pulse could be distinguished as a small, hardly perceptible thread, beating slowly. Immediately artificial respiration was commenced. For a minute or two, his condition did not alter in any respect—then the lividity of the countenance increased, the pulse was no longer perceptible, and the sounds of the heart could not be satisfactorily heard. During the whole of this time, artificial respiration had been diligently employed, but still the air appeared to enter the chest very imperfectly. I despaired. I felt certain that the man was dead, and that no human aid could restore him; and if it had not been that those standing near me urged me to persevere, I believe I should then have deserted the case as hopeless. Just at this time it occurred to me to put my finger in the mouth and draw forward the tongue, in order to secure there being no impediment to the air entering the lungs. Retaining it in this position, we again began the artificial respiration, and found that then the chest was fully expanded by each inflation. After keeping it up for a minute or two, the gentleman, who had all along kept his hand on the pulse, exclaimed, to our delight, that he could again feel it—'It was just like a slight flutter that reached the uppermost of his four fingers,' all of them being placed over the course of the artery. It gradually became more distinct and firmer, and at the same time, the lividity of the face decidedly lessened. In another minute, the man made a slight inspiratory effort. I ceased directly the artificial respiration, and merely assisted the expiration by pressure upon the ribs. Another and another in-

spiration followed, and in a short time he breathed freely without assistance. The countenance became natural, and he appeared as if in a sound sleep. In half an hour, he spoke when roused; then he vomited, and complained of giddiness. In an hour afterwards, he had recovered sufficiently to walk home.

"Moments of intense anxiety appear much longer than they really are; but even allowing this, I am quite sure that, at the very least, five minutes elapsed from the time when the man ceased breathing before the first inspiratory effort took place, and that for not less than one minute the pulse was imperceptible, and the heart's action almost, if not altogether, inaudible."

"*Case* 4. A few weeks after the occurrence just described, I was assisting Mr. Syme in removing the breast of a lady. A gentleman, my superior in the hospital, was conducting the inhalation of chloroform. Anæsthesia was complete, and the breathing good, when the operation commenced. The chloroform was allowed to remain over the face during the whole time of its performance. Before it was over, I noticed the respiration become very quick and incomplete, and suggested, in consequence, the propriety of removing the handkerchief. My remark was neglected for eight or ten seconds, and then, just as it was taken away, the breathing ceased suddenly. The face became deadly pale; the eyes vacant; the lips livid. Instant dissolution appeared inevitable (the pulse was not felt). Artificial respiration was immediately commenced, but the air not entering the lungs freely, the tongue was pulled forwards, and retained so by the artery forceps. The chest then expanded freely with each inflation, the air escaping with a cooing sound. In rather less than a minute, the respiratory movements recommenced, but at first so slowly and imperfectly that it was necessary to assist expiration. When recovery was a little more established, the operation was completed. Before the putting in of the sutures, sensation had partially returned, and in a short time the lady had perfectly recovered."

Mr. Bickersteth very properly adds: "There can be no doubt, that in the foregoing cases, a grievous error was committed by continuing the inhalation after anæsthesia was produced, and that it was in consequence of this, the accidents, so nearly fatal, occurred."

As these accidents seem to have occurred from continuing the inhalation too long, they differ entirely from nearly all those which are actually fatal, and which, as we have seen, arose from the too great concentration of the vapour, and not from any want of care in watching the patient, so as to be able to leave off at the right moment, if it were possible. I have previously stated, that after breathing vapour of the proper strength for inhalation, animals may always be readily restored by artificial respiration after the breathing has ceased, provided the heart is still beating. In the cases related by Mr. Bickersteth, the heart had ceased to beat before the patients were restored; but in the third case, there is distinct evidence that the heart continued to beat for four minutes after the breathing had ceased. It was, therefore, certainly not paralyzed by the direct action of the chloroform. The patient was nearly in the condition of a drowned person, where we know that there

is a good prospect of recovery by artificial respiration during the first few minutes after the breathing has ceased, even if the action of the heart be imperceptible. In the other three cases, also, it is probable that the breathing ceased before the action of the heart; and, at all events, this organ was not paralyzed so thoroughly as in the cases in which artificial respiration was promptly applied without effect.

Several other cases have been related in the medical journals in which patients have been restored by artificial respiration, after animation had been suspended, more or less completely, by chloroform; but the above remarks would, I believe, be applicable to all these cases.

Where patients have recovered under the use of other measures, without artificial respiration, it is probable that animation was not completely suspended, and that the recovery was spontaneous.

M. Delarue related a case of accident from chloroform to the Academy of Medicine, on August 20th, 1850, which was apparently of this nature. After administering the vapour, and when he was about to divide some sinuses in the thigh, he found that his patient (a woman) was in a state of collapse, and the breathing and pulse, "*pour ainsi dire*", insensible. The face was injected, and there was a bloody froth at the mouth. The uvula was titilated, and there was immediate movement of the eyelids, which was soon followed by copious vomiting, and the patient recovered.*

Such measures as dashing cold water on the patient, and applying ammonia to the nostrils, can hardly be expected to have any effect on a patient who is suffering from an overdose of chloroform; for they would have no effect whatever on one who has inhaled it in the usual manner, and is merely ready for a surgical operation, but in no danger. I have applied the strongest ammonia to the nostrils of animals that were narcotized by chloroform to the third or fourth degree, and it did not affect the breathing in the least. They recovered just as if nothing had been done. It is difficult to suppose a case in which the breathing should be arrested by the effects of chloroform whilst the skin remained sensible, yet it is only in such a case that the dashing of cold water on the patient could be of use. There is, however, no harm in the application of this and such like means, provided they do not usurp the time which ought to be occupied in artificial respiration; for this measure should be resorted to the moment the natural breathing has entirely ceased.

I have seen only two cases in which the patients seemed in imminent danger from the direct effects of chloroform. One of these occurred in 1853. It was the case of a child, aged six years, but small and ricketty, which had the greater part of the eyeball removed on account of melanotic disease. The usual inhaler was employed, and when the child seemed sufficiently insensible, it was withdrawn. The operation was commenced by introducing a large curved needle, armed with a thick ligature, through the globe of the eye, in order to draw it forward. As the needle was introduced, the child cried out a very little, and thinking the parents, who were in the adjoining room, would be alarmed, I poured some undiluted chloroform hastily on a rather large sponge, and placed it over the nostrils and mouth. The

*L'Union Médicale, 1850, p. 411.

sponge became pressed by the surgeon's hand closer on the nose than I intended, but it was removed after the child had taken a few inspirations. The operation was quickly concluded without any further sign of sensation than that mentioned above. At the end of the operation, the breathing was natural, but the face was pale, and the lips blue, and the limbs were also relaxed. I tried to feel the pulse at the wrist, but did not discover any. The chloroform had at this time been left off half a minute at least. The pallor and blueness continued, and in a little time the breathing became slow and embarrassed, and appeared about to cease altogether, the pulse being still absent. The windows were opened, and cold water dashed freely on the face. The child made gasping inspirations now and then, but they did not follow immediately, or seem connected with each application of the water. The gasps became more frequent, till the breathing was thoroughly reestablished, when the colour returned to the lips, and the pulse was again felt at the wrist. In a minute afterwards, the child was red in the face, and crying violently from pain, which was relieved by a little more chloroform. It appeared to be a minute or a minute and a half from the time when the sponge with chloroform was removed, till the breathing became of a gasping character. There is no doubt that in this case the heart was paralyzed, or nearly so, by the chloroform, and that its action was restored by the spontaneous gasping inspirations of the child. The accident could have been prevented by having the chloroform, which was put on the sponge, diluted with spirit.

The other case occurred in the latter part of 1852. I have no notes of it, as it took place at the beginnning of an illness, which prevented me from writing for some time; but I recollect the chief particulars of it sufficiently well. The patient was a lady rather more than sixty years of age, rather tall and thin. She required to have a polypus removed from the nose. Mr. Fergusson, who was about to operate, was nearly an hour after the appointed time, and during this interval she was pacing up and down the room, apparently in a great fright. She was placed in an easy chair for the operation, and the pulse was small and feeble when she began to inhale. Nothing particular occurred during the inhalation, but just at the time when the patient was becoming insensible, the breathing ceased, and the pulse could not be felt. She appeared to have fainted, and was immediately placed on a bed which was in the room. I applied my ear to the chest, but could hear no sound whatever. Mr. Fergusson applied his mouth to that of the patient, and with a very strong expiration, inflated her lungs, so as to expand the chest very freely. I immediately heard the heart's action recommence with very rapid and feeble strokes, as I had so often heard it recommence in animals. The patient soon began to make distant gasping inspirations, and the natural breathing and pulse were soon reestablished. Mr. Fergusson made only one or two inflations of the lungs after the first one, which of itself was the means of restoring the patient. It was about twenty minutes, however, before she became conscious; and during the greater part of this time there were spasmodic twitchings of the features and limbs on one side. In about an hour, she was pretty well; and on the following

day the operation was performed without chloroform.

The most ready and effectual mode of performing artificial respiration is undoubtedly the postural method, introduced by Dr. Marshall Hall a little time before his death. It consists in placing the patient on the face and making pressure on the back; removing the pressure, and turning the patient on his side and a little beyond; then turning him back on the face and making pressure on the back again; these measures being repeated in about the time of natural respiration.

Whether the artificial breathing is successful or not must depend chiefly on the extent to which the heart has been paralyzed by the chloroform, as was previously observed. The fact of the breathing continuing after the action of the heart has ceased, in some of the fatal cases, shows that the heart may be so paralyzed as not to be readily restored by the breathing. It is probable that in all cases in which artificial respiration can restore the patient, its action would be very prompt; still it is desirable to persevere with this measure for a good while.

As already stated, there is every reason to conclude that the right cavities of the heart are distended with blood, in all cases of suspended animation by chloroform, and therefore it would be desirable to open one of the jugular veins if the artificial respiration does not immediately restore the patient. In opening animals, just after death from this agent, I have observed the contractions of the heart to return, to a certain extent, when the distension of its right cavities was diminished by the division of the vessels about the root of the neck. Opening the jugular veins has been resorted to in a few of the cases of accident from chloroform, but hitherto without success.

I have not succeeded in restoring an animal from an overdose of chloroform, by means of electricity, in any case where I felt satisfied that it would not recover spontaneously; and I have not heard of any patient being restored by its means. For keeping up respiration, mechanical means, such as the postural method, are better; as they cause air to enter the lungs without exhausting the remaining sensibility. If electricity be used, it should be directed towards restoring the action of the heart. It is probable that the electric current would not reach the heart without the help of the acupuncture needle; but it would be justifiable to use this in a desperate case, when other measures had failed. The needles should be coated with wax, or some other non-conductor of electricity, except near the points.

In the fatal cases Nos. 40 and 48. previously related, the action of the heart partially returned during the efforts that were made for the restoration of the patient, but did not become thoroughly re-established. It is probable that the circulation through the coronary vessels of the heart was not restored in those cases, or else the blood which must have been freed from chloroform, in its passage through the lungs, would most likely have enabled the heart to recover completely. Dr. Cockle has expressed the opinion, which is very probable, that the blood enters the coronary arteries in a retrograde manner, during the diastole of the ventricles, when the aorta and other great arteries are contracting on their contents; if so, with a very feeble circulation, the

elasticity of the aorta, perhaps, cannot sufficiently act to cause a backward current; and perhaps, also, the over-narcotism of the heart is itself an obstacle to the coronary circulation, on account of the congestion of the capillaries which always attends on narcotism.

The knowledge how seldom anything effectual can be done for a person who has inhaled a dose of chloroform from which he would not spontaneously recover, ought to impress the rule very strongly on every one, to use the greatest care in its administration.

EFFECT OF CHLOROFORM ON THE RESULT OF OPERATIONS

Besides the great benefit conferred by chloroform in the prevention of pain, it probably confers still greater advantages by the extension which it gives to the practice of surgery. Many operations take place in children which could not be performed in the waking state; excisions of joints and tedious operations for the removal of necrosed bone are often performed on persons who would be altogether unable to go through them except in a state of anæsthesia; and the moving of stiff joints by force is an operation now frequently performed, although it would probably not have been thought of if narcotism by inhalation had not been discovered. The surgeon also obtains the ready assent of his patient to a number of other operations, where it would either not be obtained at all, or not at the most favourable time, if the patient had to suffer the pain of them.

The effect of chloroform cannot fail to be favourable, to a certain extent, in large operations. The patient is in a more tranquil and cheerful condition after the operation, than he would be in if he had suffered the pain of it. His pulse is usually of the natural frequency; and after an amputation, there is generally an entire absence of the starting of the stump, which was formerly so distressing. After all the minor operations in which chloroform is used, and which according to my experience comprise at least one-half of the cases, there is never a death; and the only inconvenience is a troublesome sickness of stomach in a very few instances. Moreover, when patients die after the more formidable operations, they succumb to causes which are well known, and were in operation before the practice of anæsthesia. I only know of a very few instances where there has been a reasonable doubt on the mind of the surgeon, whether the chloroform may not have had some share in preventing the recovery of the patient, after a severe operation. These were cases in which the sickness, which occasionally follows chloroform, continued for three or four days, indeed till the death of the patient. This is a point which it would be difficult to decide, for the latter part of the sickness might depend on the sinking state of the patient, and might have come on if chloroform had not been used. Moreover, as sickness is seldom very prolonged after chloroform in minor operations, except in persons who are not in a good state of health, it is most probable, that the patients who died after a great operation with continued sickness, would not have done well if no chloroform had been used.

(*To be continued*)

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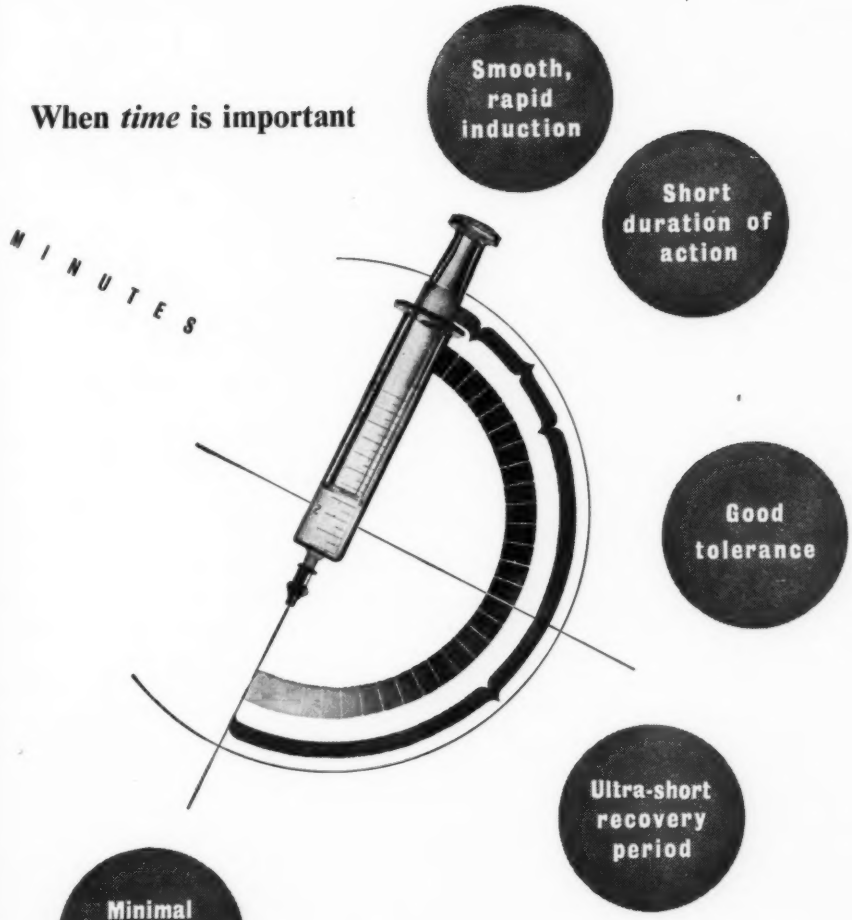

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME XXIX No. 10 *Published monthly* OCTOBER 1957

Annual subscription (post free): Inland £3 15*s.*; *Overseas* £4 4*s.*; *U.S. and South Americas* $12.00

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JOHN SHERRATT & SON *Publishers* PARK ROAD ALTRINCHAM ENGLAND

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